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Postgraduate Medicine

SPECIAL ARTICLES

Duke University School of Medicine

WILBURT C. DAVISON, M.D.
WILLIAM M. NICHOLSON, M.D.
Guest Editors

Foreword

DUKE University School of Medicine appreciates the invitation to contribute the articles for this issue of POSTGRADUATE MEDICINE. Postgraduate medical education is as important as undergraduate education for good medicine. Duke does not limit itself to the training of its own students and staff, but extends to the members of the medical profession the benefit of everything it has. Since its opening on July 21, 1930, every practicing physician has been welcomed at all clinics, and postgraduate externships for one or two weeks have been available. Methods are constantly being studied to encourage generalists to utilize postgraduate opportunities. Most family doctors intend to take postgraduate work each year, but, like house repairs, the efforts are postponed. This medical journal, POSTGRADUATE MEDICINE, brings postgraduate training to these physicians who are too busy to leave their practices.

Therefore, Duke University School of Medicine is doubly happy to accept this invitation, first because of the honor of being invited, and second because it helps to carry on the program of postgraduate medicine in which all of our medical faculty are greatly interested.

Dr. William M. Nicholson, who shares with me the honor of being a guest editor, has been in charge of the refresher courses for general practitioners for the last 15 years. The course is repeated twice annually, in March and June, and the program is held in conjunction with a North Carolina organization of general practitioners, a group which has greatly stimulated interest in the advantages of general practice and the need for more and better postgraduate medical education.

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Respiratory Resuscitation

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RESUSCITATION has been defined as "the restoration to life or consciousness of one apparently dead." In broader terms, it might be conceived as the application of measures that will tend to revive a diminished or flagging respiratory or cardiovascular function. In this paper, only that phase of resuscitation associated with the respiratory system will be considered.

The Comatose Patient

Regardless of the etiologic factors involved, the immediate problem in the comatose patient is to correct cyanosis by restoring adequate oxygenation to the blood and tissues. A good example is a patient who has taken an overdose of a barbiturate drug. When first seen, he may be lying on his back. Respirations are shallow and appear ineffective. There is very little movement of the chest during attempts at inspiration, or the thorax sinks inward during inspiration due to the pull exerted by the diaphragm. Cyanosis may be present, and one can hear stertor and gurgling in the throat as the patient is approached.

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In such a situation, a graduated form of endeavor may be followed. This will indicate not only the degree of coma, but also the extent of remedial measures which may be necessary. First, the angle of the jaw should be raised to see if lifting the relaxed tongue up out of the pharynx will improve respiratory exchange. This maneuver also determines the degree of relaxation of the jaw. If breathing becomes easier and if stertor is heard no longer, it is probable that the tongue is a principal obstructing influence. To prevent the tongue from causing further trouble, an oropharyngeal airway can be inserted. If the patient is not in deep coma, this airway may not

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be tolerated. Then, one may substitute a nasopharyngeal airway, which causes less reflex reaction. Sometimes, both types of airway are necessary.

Although pharyngeal obstruction is relieved, respirations may still be labored, and the presence of secretions may be indicated by gurgling sounds. Efficient aspiration of the pharynx may remedy this situation temporarily. A urethral suction catheter having several holes in its tip should be passed through both the nasal passages and the mouth. Coughing and swallowing reflexes induced by this aspiration are a further indication that the coma is not too profound. At this stage, the patient will be helped considerably if he is turned on his side.

If the patient exhibits no reflexes with pharyngeal aspiration, and if auscultation still reveals the presence of secretions, steps must be taken to aspirate the tracheobronchial tree. This maneuver is perhaps most easily accomplished by inserting an endotracheal tube blindly down through the nose into the trachea, and then passing a soft urethral suction catheter through it intermittently to aspirate secretions from the bronchi. Intermittent aspiration is important, for, if suction is continued too long, air will be sucked from the lungs in considerable quantities and the hypoxia from which the patient is already suffering will be increased. It is wise to administer oxygen to the patient between aspirations.

If there is no reaction to intubation or with aspiration, one knows that coma is profound and that the patient will have no subjective control over the elimination of his secretions. In such instances, it is advisable to leave the endotracheal tube *in situ*. In this way, free exchange of gases will be insured constantly, and it will be relatively easy for the attending nurse to aspirate secretions at regular intervals. Endotracheal tubes should be changed every 12 to 24 hours because secretions harden on their inner surfaces and decrease their diameters. If profound coma persists for more than 24 hours, a tracheotomy should be considered seriously.

If secretions still persist in the lung after thorough tracheobronchial toilet with a urethral catheter, bronchoscopic aspiration under direct vision may be employed to advantage.

Respiratory Insufficiency

A problem with some aspects of similarity to that of profound coma occurs in patients with severe chest injuries, traumatic injury to the cervical segment of the spinal cord, bulbar poliomyelitis or myasthenia gravis. Not infrequently, the pharyngeal and laryngeal reflexes become obtunded very rapidly, and with the associated weakening of the intercostal muscles the airway then becomes obstructed, secretions accumulate and ventilation becomes inadequate. Endotracheal intubation and frequent aspiration through the tube will relieve the situation temporarily. But since the incapacity may persist for several weeks, a more permanent solution must be found. Early tracheotomy is of benefit in these cases.[1,2] If it is done soon enough, permanent cerebral anoxic changes can be avoided. The time to do a tracheotomy is when one is in doubt as to whether it should be done.

Acute Laryngotracheobronchitis

Another distinct problem in resuscitation occurs with children who have acute laryngotracheobronchitis. The picture is a striking one—an acutely ill, febrile child who has marked upper respiratory obstruction and breathes with extreme effort. Restlessness resulting from anoxia is marked, cyanosis may be severe, and the arterial anoxemia has caused extreme tachycardia. Direct visualization of the larynx shows marked inflammation and edema of the supraglottic or subglottic structures, and sometimes of both.

This condition demands rapid action if the patient is not to suffer permanent cerebral damage. Sedatives and narcotic drugs should be given with extreme caution, as they tend to accentuate the hypoxia already present. If the child's color is good, fatigue not too severe, respirations fewer than 40 per minute and pulse rate less than 160 per minute, massive antibiotic therapy may be administered and a CROUPETTE® (figure 1) may be used. The Croupette is an apparatus capable of supplying close to 100 per cent humidity

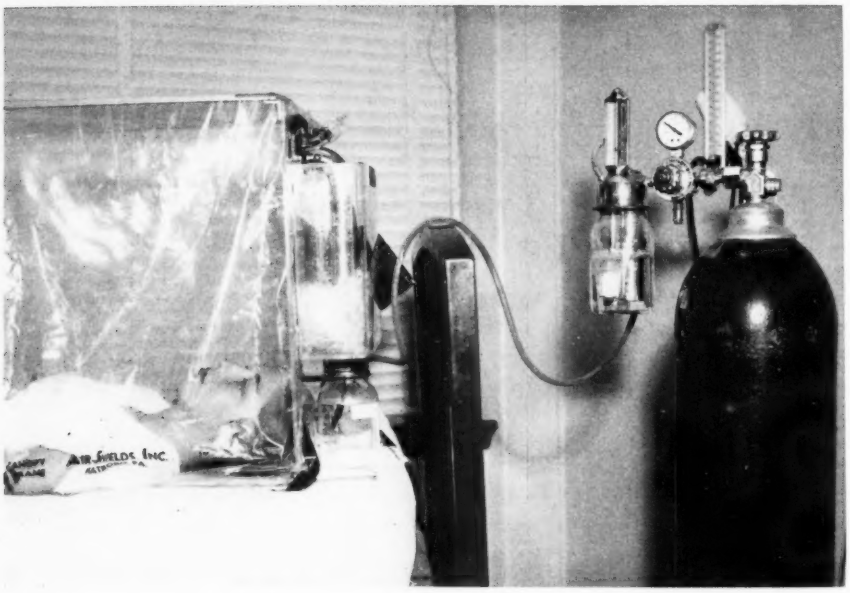

FIGURE 1. The Croupette utilizes a Venturi principle to provide high degrees of humidity with oxygen concentrations up to 50 per cent.

with 50 per cent oxygen at regulated temperatures. The inhalation of highly humidified atmospheres is of marked value in reducing edema and inflammation of the upper respiratory tract.

If the child's condition is critical, no time should be lost in performing a tracheotomy, for death in these cases results from obstructive anoxia. This operation may be transformed from an emergency procedure on a restless, moving target to an elective procedure on a quiet, peaceful child by prior insertion into the trachea of an endotracheal tube or a bronchoscope. The re-establishment of a clear airway, associated with the improved oxygenation, produces a placid patient who usually falls off to sleep. Tracheotomy is performed under local analgesia with equal parts of nitrous oxide and oxygen administered through the tube. In three or four days the inflammation and edema will have receded and the tracheotomy tube can be removed.

Oxygen Therapy

Patients in respiratory distress usually benefit from oxygen therapy, but it is important first to establish a free exchange of gases between the lungs and the atmosphere, so that

FIGURE 2. Bag and mask administration of oxygen permits concentrations close to 100 per cent.

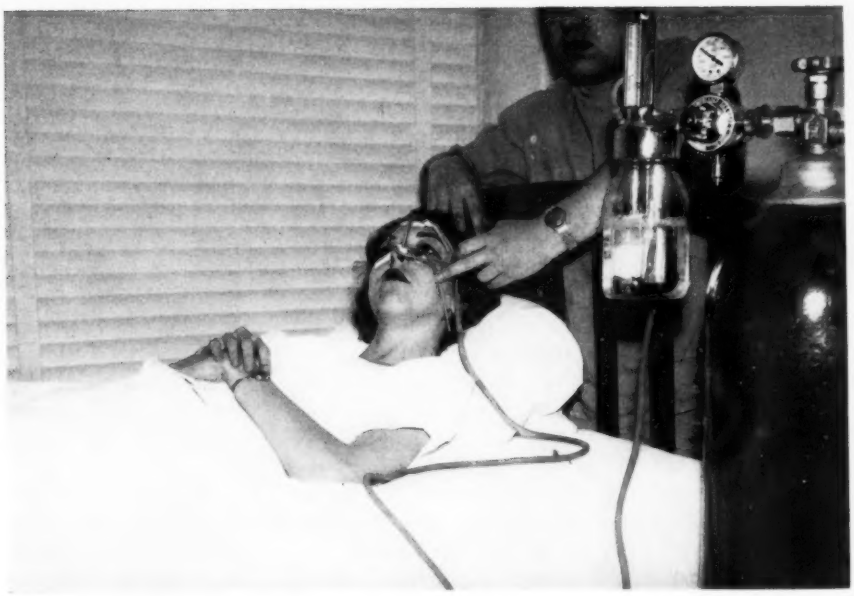

FIGURE 3. Method of determining placement of nasopharyngeal catheter for oxygen therapy.

when oxygen is given there is assurance that it is penetrating to the alveoli and blood stream.

Oxygen may be given in a variety of ways, and with varying degrees of efficiency. Concentrations approaching 100 per cent are obtained when an anesthetic bag and face mask are used. Such concentrations are indicated for short periods when cyanosis is severe and rapid oxygenation is desired. If respirations are shallow and inefficient, augmented ventilation, and hence greater penetration of oxygen to the alveoli, result when the administrator squeezes the reservoir bag synchronously with inspiratory effort (figure 2).

If concentrations of 70 to 80 per cent oxygen are desired for some time, an oronasal BLB mask can be employed. It is used efficiently only when fitted snugly to the face and when oxygen is being delivered at such a rate that at no time during the respiratory cycle does the reservoir bag collapse completely. A flow of 10 to 12 l. per minute may be required.[3] If the patient is restless and will not tolerate a mask, similar concentrations of oxygen may be obtained by use of a small, hard plastic tent.

If concentrations of 35 to 40 per cent oxy-

FIGURE 4. Positive-pressure mask (O. E. M.) for use in treatment of pulmonary edema.

gen are considered adequate for the patient, a nasopharyngeal catheter may be employed. A No. 12 or 14 urethral catheter, with several holes in the tip, should be inserted through the nose into the pharynx, a distance which corresponds to that between the tip of the nose and the tragus of the ear of the patient (figure 3).[4] Inserting the catheter only 2 or 3 in. into the nose delivers very little oxygen to the lungs. The flow rate of humidified oxygen through the catheter should be 5 to 7 l. per minute.

Large oxygen tents do not give reliable concentrations of oxygen because of the many potential sources of leakage and the large flows necessary to keep the tent replenished. Rarely will such an apparatus provide more than 40 per cent concentration, and it will do so only with flows of 12 to 15 l. per minute.

In patients with pulmonary edema, not only must high concentrations of oxygen be administered, but also efforts must be made to prevent continued exudation of fluid across the alveolar membranes and thus re-establish adequate oxygen exchange. In addition to general measures such as raising the head of the bed, bloodless phlebotomy and sedation, these aims can be accomplished by having the patient breathe oxygen intermittently through a positive-pressure mask (O.E.M.) (figure 4). The positive pressure is applied to the respiratory tree during the exhalation phase of respiration, thus tending to prevent further exudation of fluid. If the oxygen being delivered to the patient is bubbled through 95 per cent alcohol, the pulmonary edema fluid is rendered less frothy, with consequent improvement in alveolar oxygenation.

The importance of humidity with oxygenation has received increasing attention in recent years. Oxygen as it comes from a tank is bone dry and requires the addition of water vapor in order to prevent irritation of the respiratory mucous membranes. The smaller the bubbles of oxygen created by the humidifying apparatus, the greater will be the degree of humidity provided. In tracheotomized patients, in acute inflammatory conditions of the respiratory tract, and when bronchial secretions are thick and viscid, oxygen atmospheres with a particularly high degree of humidity are of considerable value. Special types of apparatus (Croupette) have been developed which will deliver saturated oxygen vapor as a fine visible mist or as an invisible mist (high-humidity oxygen tents). The concept of high-humidity rooms for emergency respiratory problems is attracting interest at present throughout the country.

It is often difficult to determine whether a patient receiving oxygen actually is deriving any benefit from it. Pink mucous membranes and fingernails are of some positive value. A more reliable guide to indicate adequate oxygenation is a gradual reduction in the pulse rate toward a normal level. If tachycardia persists with oxygen therapy, it is likely that the oxygen is not of sufficient concentration, or is not reaching the alveoli and blood stream.

Resuscitation in the Operating Room

Resuscitation of the anesthetized patient who suddenly and unexpectedly stops breathing on the operating table, perhaps during a tonsillectomy, is a task requiring alacrity and speed. In the adult, and even sooner in the child, permanent cerebral damage will occur after three minutes of complete anoxia, and fatal myocardial damage (cardiac arrest) will occur in another minute or two. When respirations stop unexpectedly in the cyanotic patient, little is to be gained by frantically compressing the chest wall or flinging the arms back and forth above the head. Nor is there time to look for a mechanical resuscitator. What is needed is a patent airway and some means of getting oxygen into the blood stream. The most ready means of therapy is to try mouth-to-mouth respiration. If the airway is clear, the thorax will move upward with this maneuver. The well-trained anesthetist will have a laryngoscope and an endotracheal tube at hand and can render the airway patent by placing a tube in the trachea. He also will have a ready source of oxygen at hand. These are the tools which are necessary for restoring respiratory function in the operating room.

In some cases, the respiratory failure may be secondary to acute laryngospasm. In such cases, it may be difficult to open the mouth

and impossible to insert a tube through the tightly closed larynx. The administration of oxygen under positive pressure by means of an anesthetic bag and mask often serves to dispel the laryngospasm. If a trained anesthesiologist is present, and a vein is open, the injection of a rapidly acting muscle-relaxant drug, such as succinylcholine chloride, may be lifesaving. It should be realized, however, that such therapy will not only relax the spasm, but also prevent spontaneous respirations by the patient for several minutes. When such therapy is not feasible, a large-bore needle, No. 13 or 14, pushed through the cricothyroid membrane into the trachea may relieve the acute emergency.[5] The remaining alternative is to do an emergency tracheotomy rapidly.

Summary

A review has been presented of some of the problems in respiratory resuscitation which from time to time confront the doctor in practice. The necessity of a clear airway, the importance of adequate ventilation of the lungs, and the administration of oxygen in adequate concentrations have been emphasized. Alert and rapid action often will save a life, or preserve the mental acuity of a patient.

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DUKE UNIVERSITY SCHOOL OF MEDICINE

Diagnosis and Treatment of Carcinoma of the Prostate

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DURING the last 15 years considerable progress has been made in the diagnosis and therapy of inoperable carcinoma of the prostate. On the other hand, diagnosis of early carcinoma of the prostate which may be cured by the radical operation has not been improved. It is this type of lesion which urologists have brought to the attention of the general practitioner into whose hands usually falls the diagnosis of this early lesion. Since this point has been stressed greatly during this time, we are seeing more of the operable or early lesions than ever before. Therefore, in years to come, our statistics on the cure of cancer of the prostate by radical operation should be more encouraging. Years ago, when life expectancy of males in the United States was about 50 years, carcinoma of the prostate was infrequently encountered. However, with the improvement of national health, the life expectancy of males has risen from 46 to 50 years in 1911 to 68 to 69 years in 1953. Since carcinoma of the prostate is a disease of old age, many more patients with this disease are now being seen. Several years ago, examination of serial sections of prostate glands obtained at autopsies at two hospitals revealed small areas of carcinomatous degeneration in 47 (20.5 per cent) of 229 cases in which the men were more than 50 years of age.[1]

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Because of the slow, insidious progress of the disease, it usually is not diagnosed until it has spread throughout the gland and often

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outside of the capsule into surrounding structures. Factors hindering an early diagnosis are: (1) The tumor grows slowly and does not cause urinary symptoms until rather late; (2) it usually starts in the posterior lobe, farthest away from the urethra; (3) it is often hidden by an associated benign prostatic hypertrophy. In 65 per cent of a series of 1000 cases reported by Bumpus,[2] the patients had only mild urinary symptoms; in 16 per cent of the cases, the first symptom was pain which was referable to metastatic lesions.

Early carcinoma of the prostate consists of a small nodule completely confined within the capsule of the gland with no evidence whatsoever of extension outside of the capsule or to surrounding structures. If there is any evidence of extension, the patient is not a candidate for the radical operation. Notwithstanding the magnitude of the operation, the complications which are not infrequently encountered, and the possibility of recurrence and metastasis, this operation has been used with increasing frequency in the last 10 years, and is recognized as the only possible cure for this malignant lesion. Our teaching at present stresses the importance of careful rectal examination of all older men by the general practitioner in order to detect early evidence of this malignant lesion. It is only in this way that the cure rate for carcinoma of the prostate can be raised. A comparison of the survival rates of comparable patients treated by radical operation and hormonal therapy shows little difference.

Considerable improvement in the diagnosis of advanced carcinoma of the prostate has been made in the last 15 years. By advanced we mean that the tumor has extended throughout the gland, into the capsule and possibly outside the capsule, perhaps to the seminal vesicle region, the base of the bladder, or to the rectum. A tumor frequently is found in Virchow's node. Metastasis to the deep pelvic lymph nodes is evidenced by edema of the extremities. Rectal examination reveals a stony, hard third degree induration throughout the gland, and the surface of the gland is irregular and nodular.

Roentgenographic examination may reveal evidence of metastasis. The metastatic lesions most frequently involve the lumbar segment of the spinal column or the bones of the pelvis, but they also may occur throughout the bony skeleton. The only metastatic lesion of bone may be a single, small nodule, but generalized lesions may be present. Osteoblastic lesions are far more common than osteolytic lesions.

Marked secondary anemia is suggestive of extension of the malignant lesion. Cystoscopy may be of help in revealing fixation and firmness of the prostatic urethra and invasion of the tumor under the trigone.

In 1949, one of us (E.P.A.) and Rundles[3] reported the results of bone marrow studies in 32 cases of carcinoma of the prostate. In 18 of the 32 cases, these studies revealed metastatic lesions in the bone marrow. In all of the 15 cases in which metastatic lesions were found in the marrow of the sternum, firm pressure over this bone elicited marked tenderness. Although it is generally recognized that carcinoma of the prostate metastasizes by the lymphatic channels, hematologic spread was suggested by the frequency with which metastatic lesions were demonstrated in the marrow of the sternum and other bones remote from the original tumor.

It was found that patients with metastatic carcinoma usually had secondary anemia. It seemed apparent that if the value for the hemoglobin was less than 12 gm. per 100 cc. of blood it suggested a metastasis.

Roentgenographic examination or biopsy revealed metastatic lesions in 24 of the 32 cases in which bone marrow studies were made. In 14 (58 per cent) of the 24 cases, bone marrow studies also disclosed metastatic lesions. In 14 (78 per cent) of the 18 cases in which bone marrow studies disclosed metastatic lesions, the serum acid phosphatase was increased. In 6 of the 32 cases, it was impossible to make a diagnosis of carcinoma of the prostate by rectal examination or by determining the value for the serum acid phosphatase. In all of the six cases, the diagnosis was made by finding carcinoma cells in the marrow. Hence, in an exceptional case in which the clinical diagnosis is questionable,

bone marrow studies may be of considerable diagnostic help.

In cases in which hormonal therapy is being used, repeated bone marrow studies will give clear indications, favorable or otherwise, of the course of the disease. In several cases, the neoplastic tissue in the bone marrow was greatly reduced after hormonal therapy, and the tumor cells became more benign in character. The severity of the anemia also decreased. It is evident, therefore, that bone marrow studies may be helpful from both a diagnostic and prognostic standpoint in cases of carcinoma of the prostate.

Gunn, Ayre, Coplan, Woods and Melvin[4] suggested cytologic examination of the prostatic secretion by the method of Papanicolaou. We are not enthusiastic about this method of diagnosis. In the first place, we question the advisability of massaging a carcinomatous prostate hard enough to obtain the cells. It may be necessary to massage the prostate several times in order to obtain a satisfactory specimen. The prostatic secretion must contain little, if any, pus and no seminal fluid. A careful technic is necessary to apply the film to the slide, and the specimen must be examined by an expert cytologist. We do not recommend the routine use of this diagnostic procedure because of the uncertainty of the results in the best of hands and because massage of the prostate may spread or stimulate the neoplasm. A negative finding is of no significance.

In discussing the relationship between hormones and prostatic cancer, Huggins, Stevens and Hodges[5] suggested that there might be some relationship between this disease and phosphatases. These are enzymes that are present in many organs. The alkaline phosphatases reported by Robinson[6] are present particularly in actively growing bones and cartilage. They also are present in the small intestine, adrenal glands, kidneys, liver and other organs. In certain diseases, namely, obstructive jaundice and bone diseases such as giant-cell tumor, osteitis deformans, osteoporosis, rickets, hyperparathyroidism and osteogenic sarcoma, there is a marked increase in the concentration of serum alkaline phosphatase.

Most of the alkaline phosphatase in the serum originates from bones and is normally excreted by the liver. The concentration of serum alkaline phosphatase reflects osteoblastic activity and is increased during bone formation. Osteoblastic stimulation may be due to metastasis of a prostatic carcinoma. An increase in the serum alkaline phosphatase may suggest the presence of metastatic lesions even in cases in which such lesions cannot be demonstrated roentgenographically.

The concentration of serum alkaline phosphatase does not necessarily bear any relationship to the concentration of serum acid phosphatase. However, an increase in the serum alkaline phosphatase may be of assistance in indicating osteoblastic response to an invading carcinoma, and thereby may be an index of such activity. In cases of metastatic carcinoma, the increase in the serum alkaline phosphatase usually is much greater than that of the serum acid phosphatase. After castration, the value for the serum alkaline phosphatase usually increases temporarily and then drops to normal, while the value for the serum acid phosphatase promptly drops to normal without any intermediate rise. This may be of help in certain cases in which the value for the serum acid phosphatase is normal and a diagnosis cannot be made by roentgenographic examination. If the value for the serum alkaline phosphatase is increased, and, when stilbestrol is administered as a therapeutic test, the value rises and then drops, this would seem to be evidence of metastatic carcinoma.

Although acid phosphatase occurs in many body tissues, the largest amounts are present in the prostate and in the kidneys. Proportionately, the prostate contains from 2000 to 10,000 units and the kidney from 6 to 8 units. This enzyme is formed by adult prostatic epithelium, and it can be demonstrated in normal prostatic secretion by the staining method of Gomori.[7] The exact role of this enzyme is not known. At present, its concentration in the serum is believed to be an index of prostatic secretion and, hence, of prostatic activity. It is an enzyme of adult prostatic epithelium and is not present in the primitive type of cell.

The relationship between the hormones and the concentration of serum acid phosphatase was brought out by Huggins and Hodges[8] and more recently by Scott.[9] Injection of androgen causes activity of the prostatic epithelium and an increase in the serum acid phosphatase. Administration of estrogen or discontinuing androgen causes a decrease in prostatic activity and a decrease in the serum acid phosphatase. The value for the serum acid phosphatase may be used as an index of activity of the prostatic epithelium and, hence, of the activity of carcinoma of the prostate. It therefore enables one to evaluate the results of therapy.

Since carcinoma of the prostate is a tumor of adult prostatic epithelium, acid phosphatase is present in large amounts in the tumor cells and in the metastatic lesions. Gutman, Sproul and Gutman[10] demonstrated that the serum acid phosphatase is increased in cases of carcinoma of the prostate in which metastasis has occurred. It is believed that simple invasion of the prostate is not sufficient to cause a significant increase in the serum acid phosphatase, but that extension of the tumor beyond the capsule is necessary for this increase. Osteoblastic metastatic lesions with significant bone reaction cause a greater increase than do osteolytic lesions.

Variations in the activity of acid phosphatase in cases of metastatic carcinoma depend on how prolifically the tumor elaborates this enzyme. The serum acid phosphatase was increased in 70 per cent of 119 cases in which carcinoma of the prostate had metastasized to bone, and the value for this enzyme was normal in 86 per cent of 88 cases in which roentgenographic examination did not reveal any evidence of metastasis.[3] Nesbit and Baum[11] reported that the value for serum acid phosphatase was increased in 66 per cent of a group of cases of metastatic carcinoma.

We previously have mentioned the bone marrow studies which were made in 32 cases of carcinoma of the prostate by one of us (E.P.A.) and Rundles.[3] The serum acid phosphatase was increased in 14 (78 per cent) of the 18 cases in which the bone marrow studies disclosed metastatic lesions. It is of interest that the value for this enzyme was not increased in all of the 18 cases. The value for this enzyme was normal in 8 (57.1 per cent) of the 14 cases in which the bone marrow studies did not reveal any evidence of metastasis. In the remaining six cases (42.9 per cent), the serum acid phosphatase was increased. The increase in these six cases is easily explainable since the patients had metastatic lesions somewhere but not in the bone marrow that was obtained for study.

In most of our cases of metastasizing carcinoma of the prostate, the values for the serum acid phosphatase have paralleled the general course of the disease and thus have furnished an indication of the activity of the lesion. If the value for this enzyme is increased, even in cases in which roentgenographic examination does not reveal any evidence of metastasis, it strongly suggests extraprostatic extension, and the prognosis is just as poor as it would be if roentgenographic examination had disclosed metastasis. Conversely, the prognosis is good if the value for the serum acid phosphatase is normal and if physical or roentgenographic examination does not reveal any evidence of metastasis.

Brendler, Chase and Scott[12] administered testosterone in three cases of carcinoma of the prostate. At the time treatment was started, the value for the serum acid phosphatase was increased in all three cases. Roentgenographic examination disclosed metastasis in two of the cases. A further increase in the serum acid phosphatase occurred in both of these cases but not in the case in which there was no evidence of metastasis. These authors suggested that it might be possible to detect occult bony metastasis by observing the response of serum acid phosphatase to the administration of testosterone.

It is known that there may be a slight increase in the serum acid phosphatase in other diseases of the prostate and in some diseases that are not of prostatic origin. The King-Armstrong method generally is used for determining the value of this enzyme. A value of 5 units or more is considered diagnostic of carcinoma of the prostate. At present, it is the general consensus that determination of

the value for this enzyme is one of the most important diagnostic and prognostic aids in cases of carcinoma of the prostate.

In 1953, Fishman and Lerner[13] described a new method for determining serum acid phosphatase of prostatic origin. They used a special tartrate which inhibits the prostatic component of serum acid phosphatase. The value obtained by this method is subtracted from the total value obtained by the King-Armstrong method in order to determine the acid phosphatase of prostatic origin that is present in the serum.

Cline, Burke, Cobb, Wilkinson and Johnson[14] modified the method of Fishman and Lerner by using nitrophenyl phosphate as a substrate. They reported the results obtained with the use of this method on more than 4000 subjects. They said that the critical limit for the value for the serum acid phosphatase of prostatic origin obtained by this method is 0.7 unit. If a higher value is obtained, it is suggestive of prostatic carcinoma. Values above 1.5 units were obtained only in cases of carcinoma of the prostate.

False negative values (values below 0.7 unit) were obtained only in cases in which the patients were being treated for carcinoma of the prostate. False positive values (values higher than 0.7 unit) were obtained in only a few cases. It is possible that this new method for determining the values for the acid phosphatase of prostatic origin may be of distinct help in the diagnosis of carcinoma of the prostate.

The treatment of early carcinoma of the prostate has not changed since Young advocated radical perineal prostatectomy some 50 years ago. Recently, the operation has regained favor since it offers the only hope for a possible cure. Jewett[15] reported that the mortality rate was 3 per cent in 200 cases in which radical prostatectomy was performed at The Johns Hopkins Hospital from April 1943 to April 1954. He also said that the incidence of postoperative complications had been lowered considerably during that decade. Recent advocates of retropubic prostatectomy have advocated the use of this approach in performing radical prostatectomy.

A comparison of the results of hormonal therapy and those of the radical operation shows that the five year survival rate is about the same for comparable patients. However, the 10 year survival rate is slightly in favor of the radical operation.

Jewett[15] recently reviewed the results in 127 cases in which radical perineal prostatectomy was performed at The Johns Hopkins Hospital. The five year survival rate was 48 per cent and the 10 year survival rate was 25 per cent. In the 48 cases in which gross examination disclosed extraprostatic extension at the time of operation, the 10 year survival rate was 12.5 per cent. In cases in which rectal examination did not reveal any evidence of extension, the five year survival rate was 61 per cent and the 10 year survival rate was 37 per cent. In 41 cases in which microscopic examination of the surgical specimen did not disclose any evidence of extension beyond the capsule, the 10 year survival rate was 49 per cent. This, of course, is a very select group of cases, and the results cannot be compared with those obtained with different types of therapy in other groups of cases. Indeed, the results obtained with different types of therapy often are questionable and difficult to evaluate. For instance, Jewett[15] said that biopsy did not reveal any evidence of malignancy in 50 of 91 circumscribed perineal nodules that were removed for examination. Microscopic examination revealed that 84 per cent of the grossly circumscribed malignant nodules were not strictly localized.

Since patients with carcinoma of the prostate are of an advanced age, the results of a statistical study of cases of this disease are of questionable value. Most of the patients possibly die of some other disease, and they live out their life expectancy before 5 or 10 years elapse after the operation.

Most urologists prefer to use hormonal therapy in all cases of carcinoma of the prostate. In spite of improvement in early diagnosis, the radical operation still is applicable in only a small percentage of cases. According to Jewett,[15,16] only 100 (19 per cent) of 526 patients with carcinoma of the prostate who were seen at the Brady Urological Institute

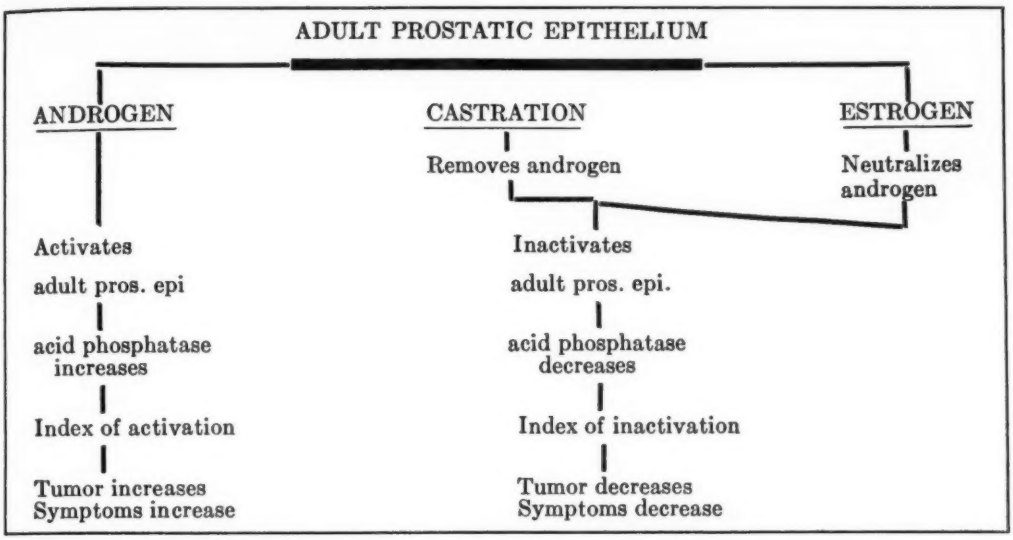

FIGURE 1. Relationship between adult prostatic epithelium and hormones.

(Reproduced from Alyea, E. P. and Henderson, A. F.: The hormonal approach to carcinoma of the prostate. II. Clinical study. North Carolina M. J. 4:212, 1943.)

from January 1949 to April 1954 were suitable for radical perineal prostatectomy.

In a large majority of the cases of prostatic carcinoma that we see, the disease is in the so-called advanced stage. It is particularly in the treatment of this stage of the disease that remarkable advances have been made during the last 15 years. The treatment always has had two main objectives: (1) the relief of urinary obstruction either by removal of the tumor or by causing its regression, and (2) relief of the severe pain caused by metastatic lesions. Approximately 40 years ago, Dr. Charles H. Mayo said: "No matter what you do for carcinoma of the prostate you do the wrong thing." By this, of course, he meant that no matter what type of treatment was used the patient's pain, discomfort and misery continued with very little relief until death. Today, such a statement would be far from the truth. At present, much can be done to improve the health and comfort of the patient.

The relationship between the prostate and the testes has been known for many years and has been the subject of considerable experimentation and dispute since the work of White in 1893. There, of course, has been conflicting evidence, but it is generally believed that castration does produce atrophy of the normal prostate and regression of prostatic hyperplasia, meaning that the prostatic epithelium is under control of the testes.

Since acid phosphatase is found in abundance in adult prostatic epithelium, withdrawal of the androgen should cause inactivation of this epithelium and, therefore, a reduction in the serum acid phosphatase (figure 1). Conversely, the injection of androgen causes activation of prostatic epithelium and an increase in the serum acid phosphatase if metastasis is present. Hence, castration or administration of estrogen is advisable in cases of carcinoma of the prostate. In cases in which treatment has been employed, repeated determinations of the value for the serum acid phosphatase are useful in determining whether or not the tumor has extended or recurred.

Various enzymes of the serum have been studied for their metabolic disturbances accompanying an active malignant lesion. Malcolm and Rusche[17] worked with chymotrypsin and rennin, and found that the equilibrium

between these two inhibitors remains rather constant but can be easily upset by any condition that produces a negative nitrogen balance. Thorough determinations of the concentration of these inhibitors are necessary to evaluate the therapeutic control of the neoplasm. These determinations permit evaluation of the results of the administration of steroids such as testosterone and progesterone in cases in which the patients have become resistant to estrogen.

The relationship between the testes, the prostate and the pituitary gland also has been known for many years. Changes in the physiology of one cause changes in the others. Hypophysectomy causes prostatic atrophy, and the administration of ANTUITRIN S® causes prostatic enlargement if the testes are present. The pituitary gland is held in check by the gonadal secretion inhibin, thus preventing overstimulation of the prostate. Hence, orchiectomy causes pituitary overactivity.

At a recent Congress of Pure and Applied Chemistry, a synthesized substance, aldosterone, which is obtained from the adrenal glands, was reported. It was suggested that this substance might be used as a biologic gyroscope to keep the vital processes of life in the proper balance. It is produced by stimulation of the growth hormone of the pituitary gland. Since a malignant tumor is a form of uncontrolled growth, it was suggested that large doses of aldosterone might inhibit the pituitary growth hormone or the cancer-stimulating hormone. Of course, the hormones that initiate cancer may be different from those that maintain it.

There is a constant balance between androgen and estrogen in the male. Estrogen withdrawal causes an androgenic preponderance and stimulates the pituitary gland to overactivity, which in turn causes prostatic enlargement. Deming[18] has demonstrated that estrogen or castration causes atrophy of human prostatic cancer which has been transplanted into the eyes of guinea pigs. He also has shown that the heterologous growth of the transplanted lesion became resistant to estrogen and that it responded in the same way as prostatic cancer does in human beings.

The use of hormonal therapy, which first was suggested by the brilliant work of Huggins, Stevens and Hodges,[5] has revolutionized the treatment of advanced carcinoma of the prostate. Physicians are all familiar with the miraculous improvement that results from use of this treatment in cases in which the patients are emaciated, pain-ridden and bedridden. The appetite improves promptly, the pain disappears, the patients gain weight, and urinary obstruction is relieved. Such improvement is the rule rather than the exception. In addition to this clinical improvement, the tumor in the prostate undergoes regression and becomes softer, the metastatic lesions of the lymph nodes "melt away," and bones that are the site of metastatic lesions undergo ossification and show new healthy cancellous characteristics.

Barnes[19] reported that the five year survival rate was 53 per cent in 31 cases of early carcinoma in which palliative treatment was used. In all of these cases, the patients were suitable candidates for a radical operation. The 10 year survival rate was 22 per cent in this group of cases. In a total of 183 cases of early carcinoma in which radical perineal prostatectomy was performed by Jewett and three other surgeons or surgical teams, the average five year survival rate was 53 per cent.[19] In the 78 cases in which the operation was performed by Jewett, the 10 year survival rate was 28 per cent. In these 78 cases, the condition of the patients was comparable to that of the patients in the 31 cases reported by Barnes in which he had a 53 per cent five year survival rate.

In 1945, one of us (E.P.A.)[20] reported that the three year survival rate was 65 per cent in another group of 40 cases in which orchiectomy was performed.

In our small group of 26 cases of very early carcinoma treated by hormonal therapy, the five year survival rate was 64 per cent and the 10 year survival rate was 30 per cent. In these cases, the value for the serum acid phosphatase was normal and there was no evidence of extension or metastasis. However, the disease was too far advanced for radical operation. A follow-up study of this group of 26

TABLE 1

CLOSED SERIES OF 26 CASES OF CARCINOMA OF THE PROSTATE—1942

Years postoperative	5	8	over 10
Contact lost	4	4	9
Patients living	13	10	5
Patients dead	9	12	12
Cause of death			
Carcinoma	2	3	3
Not carcinoma	7	9	9

cases has been made recently (table 1). Of the nine patients who died in less than five years after operation, only two died of their carcinoma. Death was due to carcinoma in three of the 12 cases in which the patients died within 10 years after the operation. In the nine remaining cases in which death occurred, the patients' family physicians informed us that the patients did not have any evidence of carcinoma at the time of their death. If one considers that the ages of the patients were 70 years or older at the time of operation and that life expectancy in that age group is 10 years, it is surprising that any still are living 12 years after the operation. When this paper was written, their ages were 82, 82, 85, 86 and 91 years, respectively. They certainly have lived out their time, and one may conclude that the treatment that was used, namely, orchiectomy and estrogen, was good for them.

We recently made a study of 258 cases of carcinoma of the prostate of all grades of malignancy treated by hormonal therapy—orchiectomy plus estrogen postoperatively. Satisfactory follow-up data were obtained for five or more years after operation in 196 of the 258 cases. In these 196 cases, the five year survival rate was 23 per cent. In 103 cases, accurate follow-up data were obtained for 10 or more years after operation. The 10 year survival rate was 6 per cent in these 103 cases. The condition of the patients in the entire group of 258 cases was not at all comparable with that of the patients in the 78 cases in which radical perineal prostatectomy was performed by Jewett or with that of the patients in the 31 cases in which palliative therapy was used by Barnes.[19] Since the disease was well advanced in all of our cases and since metastasis had occurred in many of the cases, one naturally would expect that the survival rates would be lower than they would be in cases of early carcinoma.

All carcinomas of the prostate are not dependent on the secretion of androgen. A widespread carcinoma may occur in a case in which both the testes and the adrenal glands are absent. This type of tumor is not dependent on the secretion of androgen. Other tumors require testicular androgen to continue their growth and can be controlled by a small amount of estrogen. Many tumors which at first respond to the administration of estrogen later become resistant to this hormone. Extragonadal androgen then stimulates the growth of the tumor and causes further spread. Androgenic-dependent tumors may be inactivated by a decrease in the gonadotropins of the pituitary gland and by direct action on the prostatic cells.

In 1943, one of us (E.P.A) and Henderson[21] recommended that orchiectomy should be performed in all cases of carcinoma of the prostate, but also said that an effort should be made to control the extragonadal androgen. The administration of estrogen should be started at once. We have adhered to this course of therapy for the past 12 years. In the article that has just been mentioned, it was advocated that x-rays should be applied to the adrenal glands and to the hypophysis cerebri in order to inhibit the extragonadal androgen. More recently, bilateral adrenalectomy has been tried, but we never have been very enthusiastic about the use of this procedure. During the last three years, this operation has become far less popular. The administration of cortisone probably is more suitable than adrenalectomy. Large doses of cortisone are given to prevent stimulation of the adrenal glands to produce androgen.

Nesbit and Baum[11] made a statistical study of a group of cases in which orchiectomy and diethylstilbestrol were used either alone or in combination. In the cases in which there was no evidence of metastasis when treatment was started, the combination of orchiectomy and

diethylstilbestrol was more effective than the use of either one alone. In the cases in which metastatic lesions were present, orchiectomy was more effective than diethylstilbestrol, and the combination of diethylstilbestrol and orchiectomy did not appear to be any more effective than the use of either one alone.

It is well known that exacerbations may occur in cases in which hormonal therapy is being used. In 75 per cent of our cases in which this type of therapy was used, the patients were relieved of their pain; however, an exacerbation occurred in most of these cases. In the cases in which there was no evidence of metastasis, the average duration of the remission was 57 months; in cases in which metastatic lesions were present, it was only 28 months. In cases in which an exacerbation occurs, one may try to control the extragonadal androgen by inactivating the anterior lobe of the hypophysis cerebri. This can be accomplished by hypophysectomy or by x-ray irradiation. Luft and Olivecrona[22] of Sweden reported six cases in which hypophysectomy was performed. Remarkable relief of pain occurred in all of these cases, but the long-term results are not yet available. In 1944, one case was reported[20] in which x-ray irradiation produced some improvement.

The secretion of extragonadal androgen by the adrenal glands can be blocked in three ways: (1) by adrenalectomy, (2) by application of x-rays to the adrenal glands, and (3) by medical adrenalectomy, that is, by the administration of overdoses of cortisone. In 50 per cent of reported cases in which bilateral adrenalectomy was performed, the response was favorable but was only temporary. In cases in which this operation is performed, the patients must exist on substitution therapy, and this is difficult to carry out from a practical standpoint. At present, most urologists believe that adrenalectomy has too little to offer.

In cases in which adrenalectomy is performed, the patients usually are elderly men who are in poor health and have had relapses following hormonal therapy. At best, relief can be expected to occur in only 50 per cent of cases in which this operation is performed, and the relief is limited and transient. Removal of the adrenal glands puts a severe nervous and emotional strain on the patient. The untoward effects are difficult to control by administering DOCA®. This operation seems to be most effective in cases of well-differentiated carcinoma of the prostate in which extensive metastasis occurs in spite of the fact that the primary tumor has regressed.

The secretion of extragonadal androgen by the adrenal glands also can be controlled by the application of high-voltage x-rays to these glands, but the dosage is difficult to determine.

Medical adrenalectomy (administration of large doses of cortisone) inhibits pituitary secretion of the adrenocorticotropic hormone. It is this hormone which stimulates the adrenal glands to secrete androgen. This treatment causes adrenal atrophy in rats. Prolonged administration of large doses of cortisone to men who have prostatic carcinoma may relieve the pain but it also may produce atrophy of the adrenal cortex and thus cause adrenal insufficiency. According to Kittredge,[23] Salassa and his associates found that there may be a significant reduction in the weight of the adrenal glands in cases in which cortisone has been administered for more than five days. Kittredge said that any sudden stress may lead to acute adrenal insufficiency in cases in which cortisone is being administered.

Synthetic estrogens have been used experimentally with the hope of finding one that may be beneficial in cases of carcinoma of the prostate in which the tumor is resistant to stilbestrol. TACE® has proved to be especially effective.[24] It causes fewer side effects than stilbestrol does. It seldom causes nausea, and it does not cause sodium retention, which results in edema of the extremities. The estrogenic effect of this drug sometimes occurs more promptly than that of stilbestrol, and it may be more powerful. Experimentally, it has been shown that this drug does not cause any hyperplasia of the adrenal glands as stilbestrol does, and that it does not cause any hyperplasia of the hypophysis cerebri. It, therefore, does not stimulate the secretion of androgen by the adrenal cortex. Certainly this drug is worth trying in cases in which the

tumor has become resistant to stilbestrol and in cases in which the side effects of stilbestrol prohibit its continued administration.

Since the advent of high-voltage x-ray therapy in 1922, regression of the tumor and the metastatic lesions and relief of the pain caused by the metastatic lesions have been accomplished in more than 50 per cent of the cases in which this type of therapy has been used. The introduction of radium or radon seeds directly into the involved gland or, more recently, the use of colloidal gold has given considerable promise for the destruction of the tumor and the subsequent relief of symptoms. Transurethral resection is a satisfactory procedure for the removal of obstructive tissue. If pain is not relieved by any of these procedures, alcohol may be injected into the spinal cord to destroy the sensory pathways. If this procedure fails to relieve the pain, a neurosurgeon can resect the sensory tracts of the spinal cord.

In four of our cases in which hormonal therapy was used, metastatic lesions in the lungs disappeared. In two of five cases in which complete paralysis of the lower extremities was present, there was a return of normal sensation and motor power. One patient who was paralyzed for two weeks has been walking for the last five years. Healing of the metastatic lesions of bone was evidenced by sclerosis and by smoothing and clearing of the bone detail. The tumor cells in the bone marrow undergo regression, and the characteristics of the marrow become more nearly normal. The concentration of hemoglobin in the blood also increases. These favorable responses occur in most of the cases in which hormonal therapy is used. At present attention is centered on the treatment of the androgenic-independent tumor or toward the patient with remission who has become resistant to estrogenic therapy.

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Therapy for Pulmonary and Systemic Fungus Diseases

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THIS review will be limited to the pulmonary and systemic fungus diseases and will not include infections of the hair, skin and nails, which are adequately covered in standard texts on dermatology.

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With the universal use of potent broad-spectrum antibiotics, which have brought most of the common bacterial infections under control, viral and fungus infections have assumed a position of greater relative importance. At least one fungus infection, candidiasis (moniliasis), has become more frequent and more severe as a direct or indirect effect of treatment with the broad-spectrum antibiotics.[1]

A specific diagnosis is essential for initiating proper therapy and for evaluating the improvement of the patient. Culture methods which can be applied in any routine laboratory are available.[2] In most instances, the cultivation and identification of pathogenic fungi are as easy as and, in many instances, easier than the cultivation and identification of ordinary bacteria. For certain mycotic infections, skin testing materials analogous to tuberculin can be obtained commercially, and in cases of some of the more severe mycotic infections the complement-fixation test is valuable both in diagnosis and in prognosis. This serologic test is performed in the central laboratories of many state boards of health and in the regional communicable disease centers supported by the federal government.

Specific antibiotic or chemotherapeutic agents are available for the treatment of actinomycosis, nocardiosis, blastomycosis and sporotrichosis. New agents have been used with some success in the treatment of candidiasis, histoplasmosis and coccidioidomycosis. Even a limited effect in the latter group of infections stimulates hope that specific fungicidal agents eventually will be available for the treatment of all pulmonary and systemic fungus diseases.

Actinomycosis

The infecting agent, *Actinomyces bovis*, is a normal inhabitant of the gums and tonsils of man, and produces disease most often in

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the (1) cervicofacial region, (2) lungs, (3) cecum and (4) abdominal organs. The organism is a delicate gram-positive branching filament which usually, but not invariably, produces sulfur granules in the lesions. It is anaerobic and requires a rich medium for growth. Pure cultures can be obtained from closed lesions, but rarely from secondarily infected draining sinuses. The diagnosis is usually made by finding the characteristic granules in the pus from draining sinuses, from sputum or other discharges, or by staining the organism in biopsy specimens.

Penicillin is the treatment of choice, and doses of approximately 1,000,000 units per day frequently cure the acute form of the disease. When the disease is chronic, the problem is more complex. Surgical excision and drainage are usually necessary. Potassium iodide is a useful supplementary treatment in cases of chronic actinomycosis and should be given along with penicillin or with sulfonamides for three to six months after the patient is apparently well. At the Duke University medical school, we use penicillin while the patient is in the hospital and sulfonamides in the usual doses for home treatment. A saturated solution of potassium iodide is prescribed. The initial dose is 3 drops in 30 cc. of water t.i.d., p.c. The dose is increased by one drop for each dose, each day, or a total daily increase of 3 drops, until the patient is receiving 20 to 30 drops t.i.d., p.c. After the maximal dose is reached, the amount is reduced to 5 drops t.i.d., and worked back, as described above, to 20 or 30 drops t.i.d. Penicillin or the sulfonamides can be given concurrently.

There are reports of cures following therapy with chlortetracycline, oxytetracycline, streptomycin and stilbamidine, but these agents are expensive. They are dangerous when administered for weeks and months, and are no more effective than penicillin or the sulfonamides. Occasionally, short courses of therapy with streptomycin or oxytetracycline for 7 to 10 days may be alternated with penicillin or the sulfonamides if the patient fails to respond in a satisfactory manner. Usually, however, failure to improve suggests that surgical drainage is indicated or that previous surgical drainage has been inadequate.

Nocardiosis

The etiologic agent of nocardiosis is found in the soil. *Nocardia asteroides* and several related species are capable of producing a disease which resembles actinomycosis, although the lungs and feet are more frequently involved and the cervicofacial form is rare. These species produce delicate branching filaments which are usually partially acid-fast and may be mistaken for tubercle bacilli. Sulfur granules are often found in pus from the mycetoma type of infection of the feet, but are rarely encountered in other tissues. The organisms, even from secondarily infected lesions, are aerobic and grow readily on all types of media, but, unlike tubercle bacilli, they are usually killed by the concentration processes used in the cultivation of tubercle bacilli.

In contrast to actinomycosis, nocardiosis is not affected by penicillin, even in doses of 10 to 20 million units per day. The broad-coverage antibiotics have some effect, but are much less effective than sulfadiazine,[3-5] which when administered in doses of 1 to 2 gm. every four hours maintains a blood level of 10 to 15 mg. per 100 ml. This drug usually initiates improvement in a few days. In cases of chronic nocardiosis, the treatment should be continued for six months or longer. Surgical drainage or excision of the diseased area may hasten recovery if done after initial clinical improvement from sulfadiazine therapy. We have used sulfamerazine or CANTRISIN® for home therapy after the initial treatment with sulfadiazine.

North American Blastomycosis

There are three clinical forms of this disease: (1) primary cutaneous, (2) pulmonary and (3) generalized. Secondary cutaneous lesions may appear as a result of hematogenous dissemination in the generalized form of the disease. Epidemiologic evidence suggests that the causative agent, *Blastomyces dermatitidis*, lives in the soil, but it has not yet been isolated from its natural habitat. The organism appears in the tissues as a budding, yeast-

like cell with a well-defined double contoured cell wall. The yeastlike or tissue form of the organism grows readily on blood agar aerobically at 37° C. after 7 to 14 days' incubation. The filamentous phase of the organism appears after 7 to 21 days on media incubated at room temperature. If the material to be cultured is heavily contaminated with bacteria, the addition of penicillin and streptomycin controls the bacteria without inhibiting the growth of the fungus.

Both stilbamidine[6-8] and hydroxystilbamidine isethionate[8,9] are remarkably effective in the treatment of blastomycosis, although the rate of improvement is disappointingly slow. Some symptomatic improvement with a reduction in the number of organisms in the discharges may be observed as early as 14 days after beginning therapy, but the organisms may still be cultured even after 30 days of treatment, and only slight to questionable clearing is demonstrated by x-ray examination after 30 days. During the 30 days following the cessation of therapy, most patients show a rather dramatic improvement which continues in most instances for three or four months, without further injections, until the patient is well.

The maximal daily dose of stilbamidine is 150 mg., and the total dose is in the range of 4 to 6 gm. The complications of stilbamidine therapy as recorded in the literature are (1) venous thrombosis; (2) nitritoid crises, such as sweating, nausea, vomiting, a fall in blood pressure and collapse; (3) destructive lesions in the kidneys and liver, which appear three to four months after administration of the last dose of the drug, and (4) facial neuropathy. All but the last complication can be prevented by the proper preparation and administration of the drug. Concentrated solutions are irritating and cause venous thrombosis. This may be avoided, however, by adequate dilution of the drug, and the slow administration of infusions will prevent nitritoid crises.

The destructive lesions of the liver and kidneys are caused by a degeneration of the drug which occurs when it is exposed to sunlight or even direct daylight. The drug is protected by storage in amber glass vials after manufacture. It may be weighed out safely in artificial light, but the solutions should be covered with paper while being transported to the ward, and the infusion bottles should be covered with a towel while the infusion is being administered. The neuropathy is an inherent complication for which there is no satisfactory remedy. Most of our patients have had some numbness or paresthesia in the skin of the face in the region supplied by the sensory portion of the fifth cranial nerve. The complication begins between the third and sixth month after the completion of therapy. This discomfort has been severe in only one of our cases, and in this case it is decreasing after two years.

The aromatic diamidine hydroxystilbamidine isethionate is the drug of choice since it rarely produces numbness of the face or any other symptoms when given by the proper method. The maximal daily dose established by Snapper and McVay[9] was 225 mg., and the total dose ranged from 9 to 12 gm. Each dose was diluted with 20 ml. of a 5 per cent solution of dextrose in distilled water and was administered intravenously in a period of 20 to 30 minutes. They noted venous thrombosis and occasional nitritoid crises.

In cases in which we have used this drug, an initial dose of 100 mg. in 100 ml. of physiologic saline solution was infused in one hour. On the following day, 150 mg. of the drug in 200 ml. of the fluid was infused in two hours; on the third day, 225 mg. of the drug in 300 ml. of the fluid was infused in three hours. Slow infusion of the drug is necessary. Nausea occurred in one case in which 100 mg. of the drug was infused rapidly, but subsequent injections of 225 mg. of the drug did not cause any symptoms when the infusion was given slowly.

Relapses have occurred in some cases in which the patients have been treated with either stilbamidine or hydroxystilbamidine isethionate or with both. The most obvious cause of relapse has been inadequate drainage of a circuitous sinus, especially one which is draining a lesion of the bone. Other causes for relapse which should be considered are the development in the organism of resistance to

the drug and the failure of the drug to sterilize the lesion in the presence of excessive sensitivity of the patient's tissues to blastomycin. If excessive sensitivity is suspected, a skin test should be performed with a 1:100 dilution of blastomycin or with a *Blastomyces* vaccine of comparable strength (1:1000 of yeast cells by volume), and the reaction should be read after 24 hours. If the skin reaction is 2 mm. in diameter, a 1:10 dilution of the original skin test material should be employed for desensitization. A 1:100 dilution is employed for reactions of 2.5 mm., a 1:1000 dilution for a 3 mm. reaction and a 1:10,000 dilution for a 4 mm. reaction. The initial dose of vaccine should be 0.1 ml. of the indicated dilution, and it should be administered subcutaneously. The dose is increased by 0.1 ml. every other day, or three times a week, until a dose of 1.0 ml. is reached. The next dose is 0.1 ml. of the next stronger concentration. If local erythema or induration develops at the site of the injection, the dose should be reduced by 0.5 ml. and worked up again.

Diethylstilbestrol has been used successfully by Curtis and Harrell.[10] The administration of cortisone is contraindicated since it causes a rapid dissemination of the disease.[9]

Coccidioidomycosis

There are two clinical types of coccidioidomycosis: (1) the primary type, which usually is pulmonary but occasionally may be extrapulmonary, and (2) the progressive type. In approximately 60 per cent of cases of primary coccidioidomycosis, the disease is asymptomatic and is detected only by the subsequent development of a positive skin reaction to coccidioidin. In about 1 of 100 white Caucasians and in about 10 of 100 Negroes, Mexican Indians, Filipinos and members of other dark races in whom symptoms of the primary type of coccidioidomycosis develop, the disease becomes progressive. The mortality rate in this type of the disease is approximately 50 per cent.

In the tissues, the etiologic agent, *Coccidioides immitis*, develops into a large, thick-walled spherule filled with 20 to 200 endospores. The spherule ruptures and liberates the spores which are then disseminated in the body to produce new lesions. The tissue phase or spherule-producing form can be cultivated in the yolk sac of embryonated eggs, but not on artificial media. When pus, sputum or spinal fluid containing the tissue stage of the organism is planted on media and incubated at either 37° C. or at room temperature, the filamentous phase of the organism develops after 10 to 20 days of incubation. The initial growth consists of unsegmented hyphae of moderate width,[2] but, after several weeks of incubation, characteristic rectangular arthrospores develop. These are highly infectious for both laboratory personnel and laboratory animals. This arthrospore stage is presumably the infectious stage and is found in the dust in areas in which the disease is endemic. The organism has been isolated from the soil in the endemic areas of the southwestern part of the United States.

Rest in bed is mandatory, but no specific therapy is required for the patient with a primary symptomatic infection. The sedimentation of the erythrocytes, the precipitin titer and the complement-fixing titer must be followed to detect as soon as possible the patient in whom the progressive form of the disease is destined to develop. The sedimentation rate is elevated early in the primary infection and the precipitin titer rises after 10 to 15 days. With spontaneous recovery the sedimentation rate falls to normal and the precipitins disappear from the serum. When the disease progresses, the increased sedimentation rate persists and a further increase occurs; the precipitins disappear, and the complement-fixation titer begins to rise. With spontaneous recovery from the progressive form of the disease, the complement-fixation titer falls slowly to normal. The skin reaction to coccidioidin becomes positive in 99 per cent of patients after the second week of the disease, and persists for many years except in the terminal stage of the progressive type of the disease in which it is often negative even in the presence of a steadily rising complement-fixation titer.

There is no satisfactory therapy for disseminated coccidioidomycosis. The iodides,

sulfonamides and antibiotics, including protoanemonin, have been tried without success. Sodium caprylate and ethyl vanillate are of questionable value. Of the new fungicidal agents under investigation at present, one of the more promising is prodigiosin which has cured the patients in six of nine cases in which it was used. This drug, however, is difficult to prepare, and it causes venous sclerosis and thrombosis.

Hydroxystilbamidine isethionate is as effective in inhibiting the growth of *Coccidioides immitis* in vitro as stilbamidine is against *B. dermatitidis* under similar conditions. This drug is apparently harmless when daily doses of 225 mg. are administered by the method outlined in the section on blastomycosis. Since it is probably fungistatic rather than fungicidal, one to three months of therapy would be required to produce measurable clinical improvement. In a few instances, rather dramatic improvement has been observed six months after cessation of therapy. This improvement may have resulted from the fungistatic effect of the drug or it may have been spontaneous. The ideal time to use hydroxystilbamidine isethionate would be when the first decrease occurs in the precipitin titer and when the first increase occurs in the complement-fixation titer. The treatment was started at this time in one case in which the patient, who was a Japanese physician, had been infected in the laboratory. The pulmonary lesions disappeared, and the sedimentation rate of the erythrocytes became normal in one month. In another month, the complement-fixing antibodies disappeared.

Lamb[11] apparently obtained good results by administering methyltestosterone and triple sulfonamides (sulfadiazine, sulfamerazine and sulfathiazole) in one case. Cortisone apparently causes dissemination of this infection.

Histoplasmosis

Four clinical types of histoplasmosis have been recognized: (1) the primary pulmonary type, (2) the primary mucocutaneous type, (3) the disseminated type, and (4) the reinfection pulmonary type.

In at least 95 per cent of the cases of the primary pulmonary type, the disease is asymptomatic, although x-ray examination reveals soft nodular lesions in many cases. Four or five years later, these lesions appear as miliary calcifications. After a few weeks, the histoplasmin skin test becomes positive and remains so for years. In those cases of primary pulmonary histoplasmosis in which symptoms occur and x-ray examination discloses pathologic changes, complement-fixing antibodies usually are present in the serum. They persist for a few weeks and then disappear.

The primary pulmonary type of the disease does not progress to the disseminated type in more than 1 per cent of the cases. The percentage of cases in which the primary mucocutaneous type progresses to the disseminated type is somewhat higher. The mortality rate in cases of disseminated histoplasmosis is approximately 75 per cent.

The reinfection type of histoplasmosis develops in an unknown but extremely small percentage of patients who have survived the primary pulmonary type of the disease years before, as shown by the frequent appearance of miliary calcification in the lungs. The lesions usually are situated in the upper lobe of one or both lungs and are indistinguishable clinically and roentgenographically from fibrocaseous cavitary tuberculosis caused by reinfection with *Mycobacterium tuberculosis*.

The etiologic agent of histoplasmosis, *Histoplasma capsulatum*, has been grown from the soil in areas in which the disease is endemic. The tissue form of the organism is a small, oval, yeastlike cell which lives and multiplies in the cytoplasm of endothelial and mononuclear cells. This form of the organism can be cultured from the blood in poured agar plates or on agar tubes under decreased oxygen tension and, at times, in fluid media, but shows a marked tendency to revert to the filamentous form found in nature. The filamentous phase grows readily on Sabouraud's medium at room temperature if secondary bacterial contamination is minimal. Except for the anaerobic *Actinomyces bovis*, this is the most difficult of all the fungi to culture. The addition of penicillin and streptomycin to the media is essential, and even then fast-

growing mold contaminants often overgrow the plates.

In most cases of primary pulmonary histoplasmosis, the patients recover with symptomatic treatment, which includes rest in bed. Residual granulomatous lesions in the lung have been treated successfully by surgical excision.[12] Generalized histoplasmosis does not respond to iodides, sulfonamides, known antibiotics, stilbamidine[2] or hydroxystilbamidine isethionate. Christie, Mittleton, Peterson and McVicar[13] reported that recovery occurred in 5 of 12 cases of disseminated histoplasmosis in which ethyl vanillate was used. Death occurred in all of a group of 23 cases in which the patients were untreated. Although results that have been obtained with this drug are encouraging, the dose is large and the drug is somewhat irritating to the stomach. The therapeutic dose is not much below the toxic dose.

When ANTABUSE®, the drug used in conditioning alcoholics, is added to culture media in the ratio of 1:1,000,000, it prevents the growth of *H. capsulatum*.[14] In some preliminary experiments, Drs. Isabel Christison and Norman F. Conant found that Antabuse was harmless for normal mice but apparently was toxic, at least in the doses used, for mice infected with *H. capsulatum*, since the latter animals died before the untreated controls.

When ATABRINE® hydrochloride was administered to experimentally infected mice, the survival rate was increased. In two cases in which this drug was administered in the terminal stage of the disease, necropsy did not disclose *H. capsulatum* in any of the lesions.

The growth of *H. capsulatum* in vitro is inhibited by the addition of 25 to 50 μg. of β-diethylaminoethyl fencholate (MRD-112)* per milliliter of culture medium in the presence of 10 per cent serum.[15] When this drug was administered to dogs and monkeys in daily doses as large as 10 mg. for weeks or months, it did not cause any toxic manifestations. In several cases of disseminated histoplasmosis in which the blood cultures were positive, the patients have recovered after the daily infusion of 150 mg. of the drug in 300 ml. of physiologic saline solution for 60 days. Each infusion was administered in a period of three hours. Doses of 300 mg. in 300 ml. of physiologic saline solution apparently are well tolerated, and they may produce improvement more rapidly than doses of 150 mg. The cure rate in cases in which this drug is used is not beyond the expected rate of spontaneous recovery, but the drug apparently is without harm when it is administered in the proper manner.[16]

The reinfection type of histoplasmosis, analogous to the reinfection type of tuberculosis, with cavities in the upper lobe of one or both lungs, now is being recognized. In some cases of this type of histoplasmosis, the patients have been cured by pulmonary resection.[12] Treatment with MRD-112 apparently does not have any effect on the old fibrocaseous cavitary lesions. However, since streptomycin and isoniazid have little effect on similar lesions in cases of reinfection tuberculosis, the effect of MRD-112 must be evaluated in cases of acute disseminated histoplasmosis.

The administration of cortisone may cause a rapid dissemination of the infection.[17]

Cryptococcosis

The etiologic agent of cryptococcosis (torulosis), *Cryptococcus neoformans*, has been isolated from soil, milk and fruit. It grows in the tissue as a yeastlike organism surrounded by a large gelatinouslike capsule. It grows readily on Sabouraud's medium at 37° C. after 10 to 20 days, and forms small glistening creamy white colonies which are composed of budding yeastlike encapsulated cells. The organism does not have a filamentous stage.

Cryptococcosis is usually a primary pulmonary infection but may be cutaneous, subcutaneous or mucosal. The primary pulmonary lesion may be inconsequential or never detected, and the patient may appear with a brain or meningeal lesion. Some of the recognized pulmonary lesions have been cured by surgical resection and others with vaccine, iodides and sulfadiazine.[2]

An occasional patient with cryptococcal meningitis achieves a biologic balance with the fungus and remains alive for years, but

*This drug is manufactured by The Wm. S. Merrell Co. of Cincinnati, Ohio.

the symptoms may recur periodically and the organism may reappear in the spinal fluid. An occasional patient has recovered after treatment with sulfadiazine or ACTIDIONE®.[18]

Streptothricin is effective in vitro and in experimentally infected mice, but is probably too toxic to be used in man. PROPAMIDINE® inhibits the growth of *C. neoformans* in media in the presence of serum. We have given this drug to two moribund patients who died on the third day of therapy. The patients were so ill that it was not possible to evaluate either the harmlessness of the drug or its therapeutic effectiveness.

Sporotrichosis

The etiologic agent of sporotrichosis has been isolated from plants and from infected timbers in the gold mines of South Africa. The tissue form of the organism is rarely found in human tissues but when present appears as a cigar-shaped or oval budding form. The tissue form grows readily on Francis' blood cysteine medium designed for the cultivation of *Pasteurella tularensis*. Inoculation of Sabouraud's medium with tissue or secretions and incubation at room temperature give rise to a fine filamentous type of growth on which develop small pear-shaped spores.

Most patients with cutaneous lymphatic sporotrichosis and many with generalized sporotrichosis respond slowly but satisfactorily to treatment with potassium iodide. The dose should be administered as described under the section on actinomycosis but may be increased to a maximum of 30 or even 40 drops three times a day.

A few patients are sensitive to iodides, and some patients with the generalized type of the disease respond very slowly or not at all to this therapy. It is encouraging to note that the literature contains a report of one case in which stilbamidine has proved effective. Hydroxystilbamidine isethionate should be equally effective but its use in this disease has not been reported.

Candidiasis (Moniliasis)

The etiologic agent of candidiasis is *Candida albicans*, a normal inhabitant of the mouth and intestinal tract of man. The organism in the initial culture is a budding yeast, but is found in the thrush membranes of the mouth and vagina in both the yeast phase and a filamentous or, more accurately, a pseudohyphal form. It grows rapidly in two to four days on Sabouraud's medium at either 37° C. or at room temperature, and forms a small, soft white colony filled with budding yeast cells which give off a yeastlike aroma. On subculture on cornmeal agar, typical chlamydospores develop. These distinguish the potentially pathogenic *C. albicans* from other *Candida* species that are nonpathogenic for man.

Localized lesions of moniliasis respond to a variety of well-known treatments.[2] Bronchial and pulmonary infections sometimes require desensitization and iodide therapy.

There is no effective therapy for generalized moniliasis, which usually persists for years and generally results in death. Candicidin seemed promising in preliminary studies on mice, but as yet it is too toxic for use in man. Intravenous administration of gentian violet in doses of 5 mg. per kilogram has been used in some cases of acute pulmonary or generalized moniliasis, but this drug causes venous thrombosis and no more than four to six doses should be administered.[2] DIODOQUIN® has been used in cases of acrodermatitis enteropathica in which *Monilia* were passed in the stools, but its effect in cases of uncomplicated primary generalized moniliasis has not been evaluated.

The most promising development in the therapy of candidiasis is the discovery of nystatin, a new antibiotic which is very effective in killing *C. albicans* and certain other fungi in the test tube and in experimentally infected mice. When given orally to man, it shows promise of freeing the intestinal tract of *C. albicans* and has proved effective in some types of skin disease.[19] However, in one case of chronic generalized infection of the skin and mucous membranes in which the patient, who was a child, was treated in our clinic, no improvement was noted. There is hope for the development of a nontoxic form of this antibiotic which can be used intravenously.

Geotrichosis

Geotrichum albicans, like *C. albicans*, is a normal inhabitant of the mouth and intestinal tract of man. The lesions resemble those of *C. albicans* except for the tendency to form thin-walled cavities in the lungs.[20] In the tissues and secretions, the organism has a budding form which can be mistaken for *B. dermatitidis*, but this form is accompanied by large rectangular arthrospores which have a tendency to bud from one corner of the rectangle. At incubator temperature, growth is rapid, producing a larger, rougher-looking colony than that of *C. albicans*. At room temperature, the growth is filamentous or hairy, being composed of long filaments which break up into the large rectangular arthrospores having a superficial resemblance to the arthrospores of *C. immitis* but being very much larger.

Most patients respond to therapy with potassium iodide or to the iodides after desensitization with an autogenous vaccine.

Aspergillosis

Aspergillus is ubiquitous in nature, and most species are harmless saprophytes which contaminate cultures of other organisms in the laboratory. A few species, including *Aspergillus fumigatus*, occasionally cause pulmonary disease. There are two clinical types of aspergillosis of the lungs: (1) a type of migrating pneumonitis and (2) a type in which 1 to 10 solid round lesions varying in size from that of marbles to that of tennis balls appear in the x-ray pictures. Patients with the migrating pneumonitis give immediate urticarial wheal-like skin reactions when tested with an autogenous vaccine. These patients often recover following desensitization with the autogenous vaccine. The solid ball-like lesions are usually resected because they are thought to be neoplastic. This is good therapy, but only the localized lesion should be removed, not the entire lung.

Mucormycosis

The *Mucor* fungi resemble the aspergilli in their ubiquitous nature. Pulmonary lesions, orbital lesions and lesions in the brain have been reported. In most cases the patients have been diabetics or persons who were being treated with cortisone. Surgical excision is desirable when possible after the diabetes has been brought under control or after the administration of cortisone has been discontinued. If operation is not possible, vaccine therapy should be given a trial.

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General Principles in the Treatment of Acute Burns

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ALTHOUGH there have been many changes in specific phases of burn therapy in the past decade, many of the fundamental principles remain unchanged and unchallenged because they are based on sound surgical judgment. It is doubtful whether an ideal method for treating burns ever will be developed since there are many factors which are too complex to permit stereotyped therapy. The treatment of all injuries, regardless of their type, must be individualized, but the general outline of therapy always should be based on sound judgment and fundamental surgical principles. This will encourage the physician to broaden his scope, which will allow flexibility of the general rules. The purpose of this presentation, therefore, is to outline some of the general principles in the management and treatment of burns. It is not written for the specialist, but rather for the general surgeon and physician who treats patients suffering from wounds of violence due to burns and other causes and who works in a small or medium-sized hospital where "burn teams," clinical pathologists and other highly specialized auxiliary services are not available.

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Classification

In this country, burns are classified according to their depth. A first degree burn causes erythema, and a temperature of 140° F. is necessary for its production; a second degree burn causes vesicles, and a temperature of 160° F. is necessary; a third degree burn causes charring, and a temperature of 210° F. or exposure to heat of a lower temperature for a long time is necessary. A third degree burn denotes complete loss of at least the full thickness of the skin, and possibly extends deeper in a given area.

The degree of a burn is not always easy to

HUGH CRAWFORD

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establish at the first examination. An obviously deep burn that causes charring of the skin is a third degree burn. A burn that causes the prompt formation of blisters is at least a second degree burn and may be a third degree burn. In cases of second degree burns, the inner layers of the epithelium beneath the blister survive and the skin will regenerate. Patients commonly have varying degrees of burns. In a burn that is predominantly of the third degree, there may be islands in which the burn is of the second degree, and vice versa.

Burns also are classified according to the extent of the body surface involved. The rule of 9s (figure 1) is easily remembered and is very valuable for a quick estimation of the extent of the burn.

Etiologically, burns may be classified as thermal burns, which are due to direct fire or hot liquids; chemical burns, which are due to acids, alkalis and gases, especially war gases; electric burns, and irradiation or actinic burns. Irradiation burns are of special significance as the result of thermonuclear blasts.

Treatment

The concept that a burn is an open contaminated wound that should be closed at the earliest possible moment may be applicable in cases in which the patients are civilians. However, the open air or exposure technic of treating burns according to the method of Blocker,[1] Pulaski, Artz, Schaeffer, Huckabee, Mitchell and Russel,[2] and Kyle and Wallace[3] will undoubtedly be a procedure of necessity in the event of mass disaster. At Hiroshima, a city of 300,000, the atomic bomb casualties were as follows: 80,000 dead, 40,000 injured, and 85,000 in need of medical care. Of the 85,000 who were in need of medical care, 80,000 (90 per cent) had burns. With these figures in mind, it can be readily appreciated that the following regimen of treating a single burned patient will not be applicable in the event of a disaster or catastrophe.

Owing to the disproportionately larger body surface of an infant as compared with its weight, burns are much more serious in infants than they are in older persons. A third degree burn that involves as little as one-tenth of the body surface of an infant may result in death. Infants and elderly persons tolerate burns very poorly.[4]

A burn is a toxic permeable membrane. It may be compared to an octopus which is squeezing out vital body substances such as plasma and electrolytes. It also causes destruction of erythrocytes. At the same time, it is injecting "stinger substances" which affect the circulation (increased capillary permeability with resulting hemoconcentration), the kidneys (lower nephron nephrosis due to jamming of hemoglobin), the liver (glycogen depletion and focal necrosis), the pituitary and adrenal glands (neuro-endocrine response), and the stomach and intestine (ulceration and hemorrhage). Many means and agents must be used simultaneously to treat a burn successfully. No single one will succeed by itself.

First-aid treatment consists of preventing further contamination. Dry sterile dressings should be applied if they are readily available. If they are not available, the patient or the burned surface should be covered with freshly laundered sheets or pillowcases, which are relatively sterile. The burned clothing should not be cut away, and ointments should not be applied. The patient should be hurried to the hospital.

Second degree burns frequently will cause excruciating pain because of stimulation of the injured nerve endings. In cases of third degree burns, pain occurs primarily at the periphery and it usually is not extremely severe. Severe pain does not occur in cases in which shock is present. If drugs are used in cases in which shock is present, they should

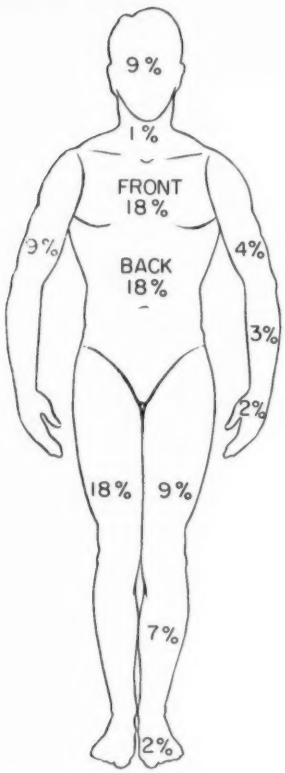


FIGURE 1. The rule of 9s for rapid estimation of surface area. The head comprises 9 per cent of the body surface, the neck 1 per cent, each upper extremity 9 per cent, the anterior torso 18 per cent, the posterior torso 18 per cent, and each lower extremity 18 per cent. If the extremities are divided, the upper arm comprises 4 per cent, the forearm 3 per cent, the hand and wrist 2 per cent, the thigh 9 per cent, the lower leg 7 per cent, and the foot and ankle 2 per cent.

be administered cautiously. Extreme pain may cause shock. DEMEROL® is somewhat safer than morphine since it does not have the same tendency to produce depression of the respiratory center when administered in effective doses. If the patient is to be transported, a responsible attendant should be advised verbally and in writing regarding the dose of any drug that has been administered. If an analgesic drug is to be given to an injured patient who is in a state of peripheral circulatory failure, it should be administered intravenously. If it is given subcutaneously or intramuscularly, it will not be absorbed until the peripheral circulation has been restored, and, if a second or third dose is administered because of persistent pain, the effect will become cumulative and the outcome may be disastrous.

When the patient is treated in the accident room, all of the personnel should wear caps and masks. The patient should be placed on sterile sheets. All of the patient's clothing should be removed, and the extent of the burn or burns should be charted. A Foley indwelling catheter should be inserted into the bladder. A specimen of blood should be obtained for chemical analysis in order to establish a base line for intravenous therapy. Blood corpuscles and serum should be obtained for crossmatching. If the initial specimen of urine is grossly bloody, it indicates the presence of a severe, extensive, deep burn. If the burn involves more than 20 per cent of the body surface, the development of shock and renal insufficiency can be anticipated.

Blood is the bulwark of intravenous therapy in the treatment of shock and extensive burns.[5-7] It will prevent shock, and it may prevent the development of secondary anemia. In cases in which blood or other fluids are to be administered intravenously, a vinylite, polyethylene or plastic tube should be inserted into the distal end of the saphenous vein to lessen traumatic or chemical thrombosis.

It might seem that transfusion of plasma would be the ideal replacement for plasma proteins which are being depleted. However, plasma that has been labeled with radioisotopes has been found to escape from the circulation into the general body fluids with great rapidity. Pooled plasma may cause homologous serum jaundice. While one unit of serum albumin has the osmotic ability to draw about 400 cc. of fluid from the tissues, it has no oxygen-carrying power.

The total amount of blood, blood substitutes or other fluid that is administered in 24 hours should not exceed 2 l. for each 10 per cent of the body surface that has been burned. Formulas for calculating the total amount that should be administered are shown in table 1. These are modifications of formulas devised by Evans,[4,5] and they are simple and accurate.

These formulas should not be applied rigidly in cases of very extensive burns. If they are applied rigidly in cases in which burns involve 50 to 60 per cent of the body surface, the calculated requirements will be excessive. We do not believe that it is advisable to administer intravenously more than 5 l. of fluid (blood, colloids and electrolytes) during the first 24 hours, regardless of the extent of the burn. We refer to this as the "dry treatment." The burn already has placed a tremendous strain on the heart, lungs and kidneys. The administration of larger quantities of fluid might cause fluid intoxication and overloading, which, in turn, might lead to cardiac insufficiency, pulmonary edema and possibly to death. We believe that it is far safer and much better to err on the "dry" side than to overtreat and overload the patient.

Patients who have renal, cardiovascular or pulmonary disease tolerate burns, even those of minor extent, very poorly. Very young and very old patients also are serious risks. We occasionally are amazed by the excellent condition of referred patients who have "thrived on neglect," and who have had relatively little intravenous therapy. If the burns are scattered, or if both second and third degree burns are present, the calculated fluid requirements may be cut in half.

The calculated requirement for blood may be cut to one-half on the second day and to one-fourth on the third day. Thereafter, blood should be administered as necessary. Although determinations of the blood volume are the best guide for fluid replacement, they are not always readily obtainable. The hematocrit reading is not always an accurate index of the need for fluid replacement, for the blood volume may be markedly reduced when a normal hematocrit reading of 45 is obtained.

Twelve hours after the intravenous administration of fluids is started, it is advisable to evaluate the patient's general condition, the fluid replacement program and the urinary output. If the flow of urine from the indwelling catheter has been maintained at an average rate of 25 cc. or more per hour, the amount of fluid that is being administered may be considered adequate. If the hourly output of urine has exceeded 150 cc. for more than three consecutive hours, too much fluid is being given. This may happen when the magnitude of the burn has been grossly overestimated. When this occurs, the amount of fluid should be cut in half. A urinary output of less than 15 cc. per hour for three consecutive hours probably indicates that an inadequate amount of fluid is being given. To correct the deficit, one should increase the fluid ration by 50 per cent. If the diminution in the urinary output results directly from in-

TABLE 1

FORMULAS FOR INTRAVENOUS THERAPY*

Blood or blood substitute:	1 cc. per kilogram of body weight for each per cent of body surface burned.
Equal parts of electrolyte solution (0.9 per cent solution of sodium chloride) and a 5 per cent solution of dextrose in water:	1 cc. per kilogram of body weight for each per cent of body surface burned.

Example—For a 70 kg. man with a third degree burn that covers 35 per cent of the body surface, the calculation would be as follows:

Blood or blood substitute:	$70 \times 35 = 2{,}450$ cc.
Equal parts of electrolyte solution and dextrose solution:	$70 \times 35 = 2{,}450$ cc.

*The amounts determined with these formulas are the maximal amounts that should be administered in the first 24 hours.

adequate fluid therapy, a significant increase should be produced by the intravenous administration of 1000 cc. of an electrolyte solution or a plasma volume expander.

Fluids may be administered orally when they are readily accepted by the patient. If oral administration of fluids is started too soon, distention, nausea and vomiting are likely to occur. It should be started gradually and increased, but it should not be increased fast enough to cause nausea and vomiting.

All burned patients should receive a "booster" injection of tetanus antitoxin or toxoid. Prophylactic tetanus-gas gangrene antitoxin also should be administered.

Penicillin and streptomycin are the antibiotics of choice in the treatment of burns. It should be emphasized that the local use of an antibiotic is not a substitute for good surgical treatment. However, the local use of antibiotics may be of value in treating invasive infection. The proper concentration of antibiotics for local application has not been determined accurately, and their use is on an empiric basis. The antibiotics have certain disadvantages when used either alone or in combination. Penicillin is destroyed by changes in the pH and in the presence of mixed infection. The incidence of local sensitivity reactions may be as high as 15 per cent.

Streptomycin is very effective against a wide variety of gram-negative organisms, but its effect may be variable, and strains that are initially sensitive to this antibiotic may rapidly develop a resistance. It also has a selective neurotoxic action on the acoustic nerve. Although THRYCIN® is effective against hemolytic streptococci and *Micrococcus albus* and *Micrococcus aureus*, it is ineffectual in cases of mixed infection with gram-negative organisms, and it even may encourage the growth of some of these organisms. Gram-negative aerobic bacteria are not susceptible to bacitracin.

Some authors have found that the local use of streptomycin and penicillin is a useful adjunct. The possibility that a sensitivity reaction may follow the repeated application of these antibiotics must be considered. Drugs are not a substitute for established surgical principles, but they may be used as an adjunct. Although bacteriologic study of the wound is of definite value, the gross appearance is the best guide to progress.

Burns Involving Special Areas

Since edema of the glottis develops very rapidly in cases in which flames, soot or steam has been inhaled, a prophylactic tracheotomy should be performed immediately. Bronchopneumonia almost always develops in cases in which a burn involves the respiratory tract. Oxygen and antibiotics should be administered in these cases. In order to prevent the development of pulmonary edema, one should avoid overloading the circulation. Morphine should not be administered because it will cause respiratory depression.

Since burns that involve certain parts of the body such as the eyes, face, hands, feet, axillae, flexion creases and genitalia are followed by crippling defects, they should be regarded as serious even if they are not extensive. The treatment of burns of the face is of particular significance because of the disfigurement such burns cause. Even slight burns of the face should be treated with grease compression dressings, as will be outlined in detail later. Since separation or sequestration of the sloughs usually occurs in cases of third degree burns of the face, surgical excision of the sloughs rarely is necessary.

Burns of the eyes demand consultation with an ophthalmologist. Cocaine causes edema and softening of the cornea. As a precaution against the development of synechia of the iris, the pupils should be kept dilated with atropine. Treatment of burns of the conjunctiva consists of the application of an ophthalmic ointment containing 2 per cent of PONTOCAINE® hydrochloride or BUTYN® sulfate and the instillation of a 1:5000 solution of METAPHEN®. If the lids, conjunctiva and globe have been burned, the raw surfaces must be kept from uniting by passing a smooth glass probe between them daily to break up any adhesions that may form.

Burns that involve the mucous membranes of the mouth and nose should be coated with NUPERCAINAL® ointment or should be painted

FIGURE 2. a, b and c. Preoperative photographs of a 10 year old girl with second and third degree burns of the hands. Although the burns were old, the hands had been dressed in a functional position—as when holding a pen or pencil. Split-thickness grafts obtained from the buttocks were used to cover the denuded surfaces in one operation.
d and e. Normal function and slight cosmetic residual approximately three years later.

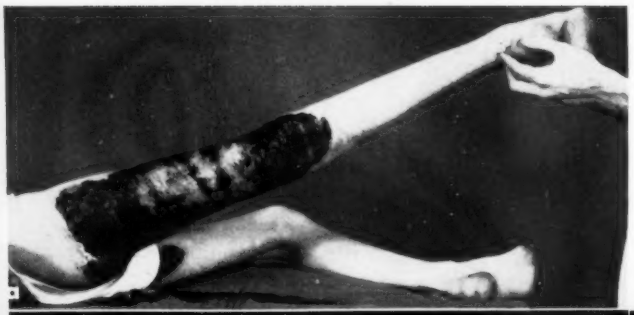
with a 1 per cent solution of NUPERCAINE® hydrochloride. Burns of the inside of the mouth are presumptive evidence that the throat has been burned. The treatment is the same as that which has been outlined for burns involving the respiratory tract.

If the hands have been burned, they should be dressed in a functional position. The metacarpophalangeal joints should be moderately flexed, and the interphalangeal joints should be slightly flexed (figure 2). Contiguous surfaces of the fingers should be separated.

In cases of burns of the genitalia, a Foley indwelling catheter should be inserted into the bladder, and grease dressings should be applied.

Local Treatment of the Burned Surface

Simplicity is the key to local treatment of the burned area, but this type of treatment should not be undertaken until the preliminary procedures outlined have been completed and until the general condition of the patient is good. It rarely, if ever, is necessary to anesthetize a burned patient. Cleansing, which should be minimal unless there is gross contamination, should be carried out aseptically. It should be done gently with mild soap and



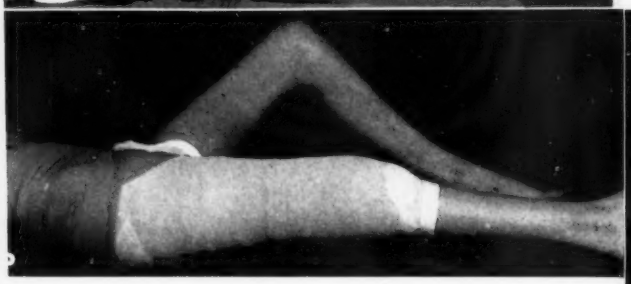


FIGURE 3. a. Photograph of a 14 year old boy with third degree burns of the thighs and perineum caused by a gasoline explosion while he was riding a tractor. b. Dry surgical rayon was placed on the burned surface. The pantaloon occlusive or compression dressing was held in place with stockinet. Since the burned areas were well circumscribed, they were débrided surgically one week after the patient was admitted to the hospital, and split-thickness grafts obtained from the posterior torso were applied on the twelfth day after the injury. c and d. Photographs taken one year later.

water. Debris should be removed with sterile instruments, and the burned area then should be flushed with physiologic saline solution. Blebs and blisters should be decapitated.

In some cases, it may be difficult or even impossible to distinguish areas in which the burn is of the second degree from areas in which it is of the third degree. The application of hydrogen peroxide frequently will prove useful for this purpose. Peroxide bubbles and foam will form over areas in which the burn is of the second degree, not over areas in which the burn is of the third degree because the skin is dead.

Occlusive dressing—Fine-mesh gauze impregnated with petrolatum should be applied so that it will extend well beyond the visibly burned surface. If rolls of grease-impregnated gauze are employed, they should be applied along the long axis of the extremities rather than in a circular manner. Rayon,* first used as a surgical dressing by Owens,[8] is an ideal dressing. It is easy to apply in large sheets, the mesh is sufficiently fine to prevent the ingrowth of capillaries and granulating buds, and it affords adequate drainage. FURACIN®-impregnated gauze is a satisfactory surface dressing although instances of sensitivity have been noted. If boric acid ointment is used, the boric acid may be absorbed and act as a cumulative systemic poison.[5, 7, 9]

When the dressing is being applied, denuded areas must not be permitted to come in contact with one another, particularly in

*This may be obtained from the Winchester Mills, Inc., 120 West Forty-second Street, New York, New York.

cases in which the burns involve the fingers or axilla. It is extremely important that the hands be dressed and splinted in a functional position. The wrist should be straight or slightly flexed; it should not be cocked up. The metacarpophalangeal joints should be moderately flexed, and the interphalangeal joints should be slightly flexed. To attain this position, the physician should place his thumb in the palm of the patient's hand. If a splint is necessary, it should be applied to the side opposite the injury.

The second layer of the occlusive dressing consists of LISCO® flat gauze sponges (4 by 4s opened up to 4 by 8s). These "flats" have an inner absorptive cotton filler. The third layer consists of thick cotton padding similar to an abdominal drainage dressing. The fourth layer consists of narrow or wide gauze rolls to hold the bulky dressings in place. KERLIX® or Krinkle gauze rolls are excellent but expensive. In cases in which the patients are children, especially in cases of burns of the perineum or extremities, a layer of cellophane or oiled silk will act as a waterproof barrier and will keep the surrounding area dry.

If elastic bandages are used as the outer layer, they should not be wrapped too tightly around the extremities, the abdomen or the chest. Old ones that have been laundered repeatedly are preferable to new ones. Stockinet, either plain or cut on the bias, is inexpensive, is easy to apply, fits snugly, does not bind or roll in the creases, and follows contours evenly (figure 3). It has many advantages over new elastic dressings, but it has none of the disadvantages of these dressings, which roll and bind in the creases and become tighter, possibly as the result of edema. Pulseless extremities have been observed after the application of pressure dressings. Pneumonia may result if the dressing limits full excursion of the chest.

Although the term "pressure dressing" frequently is used to designate this type of dressing, it is a misnomer. The pressure should not exceed 20 or 30 mm. of mercury. A better term is "occlusive dressing" or compression dressing.

Second dressing and accessory measures—The initial dressing may be left in place for five to seven days. If the dressing remains clean and if there is no evidence of infection, it may be left undisturbed for 8 to 10 days. A second degree burn should heal completely in that time, and the area of a third degree burn should be well demarcated. During the first two weeks, the patient should be watched for the development of anemia, hypoproteinemia and dehydration. If any of these complications become evident, they should be treated vigorously.

Subsequent dressings—One never should lose sight of the fact that the primary aim in

FIGURE 4. Exuberant granulations resulting from an old, neglected third degree burn of the chest and abdominal wall. Axillary contractures have already developed. Grafts applied to edematous granulations such as these will only result in failure. To prepare the area for grafting, the granulations were shaved down to a smooth base, and the axillary bands were released. TRILENE® analgesia was used for this procedure. A dry, fine-mesh dressing was applied. The entire denuded area was grafted three days later by using split-thickness grafts obtained from the buttocks.

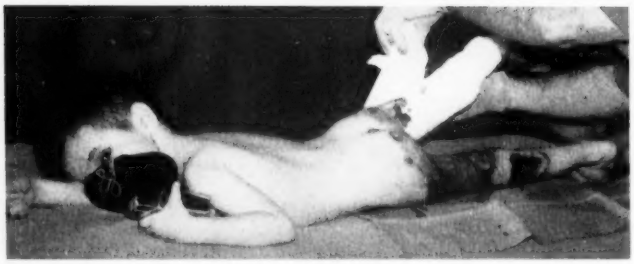


FIGURE 5. Unposed photograph showing self-induction of Trilene analgesia by a four year old boy while dressings are being removed from granulating surfaces resulting from burns. As evidenced by the child's composure, the analgesia is complete.

treatment of a third degree burn is to cover the denuded surface with skin at the earliest possible time. Before skin grafting is possible, it will be necessary to remove the slough resulting from the burn. Deep fibrous skeins of dermis can be removed by placing the patient in a saline bath. Two pounds of salt should be added to a tub of water, and the temperature of the water should be 100° to 105° F. In many cases, however, the slough is tenacious and its removal is difficult, painful and time-consuming. Some of the disadvantages of compresses and wet dressings are as follows: Infection may be introduced, and the compresses and wet dressings are painful to remove and are very messy (figure 4). Infection is much more difficult to eradicate than it is to prevent. Chemicals and various enzymes have been used to remove the sloughs. The basis for their use is empiric, and, in our clinic, the results have not been good enough to warrant their use.

The use of self-induced Trilene analgesia[10] has been a very valuable adjunct in treating many patients with severe burns (figure 5). Even a child can regulate the analgesia. A new Duke University Inhaler for the self-induction of Trilene analgesia recently has been introduced.*

We believe that the best way to remove sloughs or exuberant granulations is by shaving with a grafting knife, a Brown electrodermatome, a dermatome blade or a WECO® Webster knife.† A smooth plane can be obtained very rapidly in this manner. Light anesthesia or self-induced Trilene analgesia should be used for this procedure.

To facilitate the application of grafts either immediately or 48 hours later, irregular edges should be trimmed and cut to form essentially straight lines. All of the small epithelial islands should be sacrificed. Cold sponges applied for a few moments with firm pressure will control the bleeding. The raw surface then should be dressed with dry, fine-mesh gauze or rayon, and, except for the absence of grease-impregnated gauze, an occlusive compression dressing should be applied again.

If the shaving procedure or surgical excision has not been too extensive, it may be desirable to apply skin grafts immediately. Otherwise, it is best to wait 48 hours to give the patient a rest, to allow capillary oozing to stop, and to permit the bed to prepare itself for the reception of the grafts. Two surgical procedures of small or medium extent are better for the patient and the surgeon than one extensive procedure that might result in disaster for the grafts or for the patient.

Diet

As soon as the patient will tolerate it, a diet high in proteins, vitamins and calories should be used. The minimal daily intake of protein should not be less than 1 gm. per kilogram of body weight. A larger caloric and protein intake can be obtained by utilizing a highly concentrated feeding supplement. This is of importance in cases in which there is a negative nitrogen balance; that is, in cases in which the nitrogen excreted in the urine exceeds that in the diet. Vitamin and iron supplements are necessary in the rebuilding process since anemia is a counterpart of all severe

*This inhaler can be obtained from Ayerst Laboratories, 22 East Fortieth Street, New York 16, New York.

†This knife is manufactured by the Edward Weck Co., 135 Johnson Street, Brooklyn, New York.

burns. If the kidneys have been injured, their ability to concentrate urine will be impaired, and larger quantities of water must be made available. Under ordinary circumstances, a 5 per cent solution of dextrose will supply sufficient "available" fluid to promote urinary flow. Intestinal ulceration (Curling's ulcer) and bleeding may contribute significantly to the development of anemia. Slight bleeding may be difficult to detect, especially in cases in which iron preparations are being administered orally, since they will make the stools black. In these cases, the guaiac or benzidine test should be used to examine the stools for blood. If vomiting persists, the necessary nourishment may have to be administered by means of a nasogastric tube.[11]

Skin Grafting

Every effort should be made to apply the skin grafts at the earliest possible moment. Unless there are complicating factors, grafting should be started not later than two or three weeks after the injury. As previously stated, grafts may be applied either when the wound is prepared for the reception of the graft or 48 hours later. The extent of the area to be grafted and the condition of the patient will influence the decision. If the grafting must be done in stages, the hands, eyelids, genitalia, axillae, popliteal fossae and groins should be grafted first. A grafting operation never should be started at the end of the day. The co-ordination of aim and interest of the surgical team, the anesthetist, the blood bank physician and all operating personnel is most important.

An accurate estimation of the amount of skin that will be necessary can be made by covering the denuded surface with gauze pads (4 by 4s opened up) and by overlapping them slightly to allow for the necessary trimming and for cuts of skin that will not extend to all limits of the dermatome. Split- or intermediate-thickness grafts can be cut accurately with any of the calibrated skin-cutting devices such as the Padgett-Hood dermatome, the Reese dermatome, the Brown electrodermatome or the VACUTOME®. Thinner grafts may be necessary for children and elderly patients. One should err on the side of cutting the grafts too thin rather than too thick. The rate of "take" will be higher and the donor sites will heal in 12 to 14 days. If necessary, a second crop of skin can be cut from the same donor site in three to four weeks. Any flat surface such as the thighs, buttocks or back will serve as an excellent donor site. Except in cases of dire necessity, grafts should not be obtained from the anterior part of the chest.

After the grafts have been cut, they should be folded with the subcutaneous side inward, and should be placed in a sponge that has been moistened with warm saline solution. The sponge should be identified accurately by the scrub nurse to prevent it from being discarded. The sponge may be placed under the cover of the instrument tray, or it may be clamped to the cover.

The donor sites may be dressed with a single layer of petrolatum-impregnated gauze, Furacin, or surgical rayon, and a routine compression dressing should be applied. This dressing may be left undisturbed for 10 to 12 days, when the denuded areas should be completely healed. Donor sites on the extremities

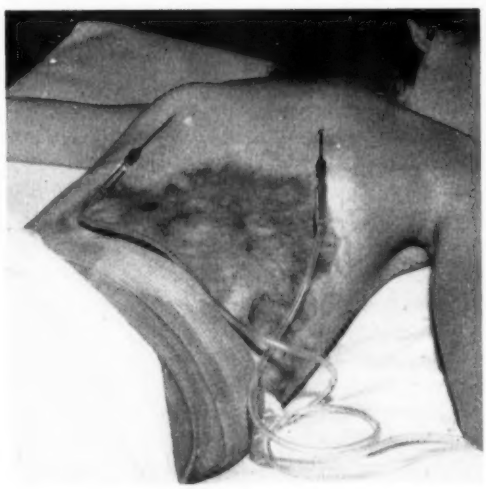


FIGURE 6. Subcutaneous infusion of physiologic saline solution to which procaine hydrochloride has been added to relieve pain will facilitate cutting of grafts in debilitated patients, especially from the back when the scapulae and ribs stand out prominently because of loss of subcutaneous tissue. The infusion should be started several hours prior to the operation.

may be exposed after several days have passed.

If the patient is debilitated or if subcutaneous tissues have been lost, the cutting of grafts may be somewhat difficult, especially from the back when the ribs stand out prominently with intervening depressions in the interspaces. To facilitate the cutting of the grafts, these depressions and others can be overcome by subcutaneous infusion of physiologic saline solution to which procaine hydrochloride has been added (figure 6).

Placement and suture of the grafts—The position of the grafts will at least have been partially planned before they were cut. The grafts never should be placed so that a vertical seam will occur on the face, neck, antecubital fossa, hand, groin, popliteal fossa, ankle or across the axilla. When one is in doubt about the best position for the placement of the grafts, they should be placed in the transverse position; however, in some cases in which grafts are to be applied to the upper arm or forearm, vertical placement may be better.

The grafts should be smoothed out with the closed end of the tissue forceps. They will stretch considerably. If the edges of the granulating surface have been prepared properly, the grafts can be sutured rapidly with a continuous suture of No. 00000 silk. To prevent tenting of the grafts, interrupted tacking sutures should be inserted, and their ends should be at least 1 cm. long to prevent engulfment and troublesome granuloma formation. If a bolus dressing is to be used, interrupted sutures of silk should be used at the periphery, and their ends should be left uncut so that they can be tied over mechanic's waste.

A few strategically placed darts or vents may be made with a No. 11 blade to permit the escape of air and fluid. Darts and vents never should be made in a graft that has been applied to the face. The space between the graft and the recipient bed should be flushed with a long blunt needle and syringe containing 10 to 20 cc. of physiologic saline solution to which 300,000 units of penicillin has been added.[12] In order for the graft to "take," it must be in apposition with the underlying bed. A single layer of petrolatum- or Furacin-impregnated gauze and a snug immobilizing compression dressing should be applied with meticulous care. A dressing that has been hastily or carelessly applied may result in loss of the graft.

Refrigerated skin—Any unused portions of grafts should be wrapped in a gauze sponge and placed in a biologic tube. The open end of the tube should be stoppered with gauze or cotton and sealed with paraffin. The tube should be marked carefully with the date, the patient's name, and the approximate amount of skin that it contains. It should be placed in or immediately below the meat tender of an electric refrigerator where the temperature is about 40° F. Freezing or quick-freezing, except by special methods,[13] will crystallize the cells and kill the grafts.

Subsequent graft dressings—The initial graft dressing should be removed on the fourth or fifth day after its application. The sutures then will have served their purpose and should be removed. If they are permitted to remain, they will only act as foreign bodies. If the grafts overlap normal skin, any overlapping portions should be trimmed away with meticulous care, since they serve as an excellent culture medium. Any secretions should be wiped dry with cotton applicators. Another grease compression dressing should be applied, and should be changed every second day for two or two and a half weeks. By that time, the graft will have matured sufficiently to permit it to be left exposed. At that time, a light application of NIVEA® creme or cold cream is beneficial to prevent drying and scaling. Burns of the legs and feet should be supported and protected with elastic dressings before and when weight bearing is begun (figure 4).

Loss of grafts—Success in skin grafting is not a matter of luck. The rate of "take" should approach 100 per cent. However, there are conditions, such as vomiting and continued soiling with excreta, which may result in the loss of a graft in a localized area. If the area is small, healing by second intention and epithelization will occur. If it is large enough to accept or warrant a graft, a refrigerated graft then can be snubbed or tacked on with sutures.

FIGURE 7. Extensive electric burns with destruction of the lower lip in a one year old child who placed a live extension cord in her mouth. Reconstruction was deferred for one year, when the mucous membrane from the inner surface of the cheeks and lip was advanced to reconstruct the lip. The postoperative photograph was made one year after the operation.

A graft is either living or dead at the time the initial graft dressing is removed. Infection is invited and time is lost by permitting a dead graft to remain. It should be removed with fine forceps and scissors. A moist or dry dressing should be applied for a day or two to permit any soiling or infection to disappear. A refrigerated graft then should be applied. If this graft is used within two or three weeks after it was cut, the "take" will be as good as that of a freshly cut graft.

Electric Burns

There are two general types of electric burns: (1) those produced by electric flashes (flash burns), and (2) those caused by the passage of an electric current through the tissues. In several respects, electric burns may be compared to gunshot wounds: (1) Examination frequently discloses a wound of entrance and a wound of exit where the part is grounded; (2) the involvement of the subcutaneous tissue frequently is greater than that of the skin, and (3) tissues that offer the greatest resistance, such as bones, joints and tendons, may suffer the greatest injury.

Flash burns may appear black owing to the arc's igniting the incandescent gases. They usually are second degree burns. Electric burns of the hands and lips of children occur when the children grasp an exposed extension cord or when they insert a safety pin into a live socket (figure 7). When moistened lips come in contact with a live plug, extensive burns of the lips and tongue result.[10] Unerupted tooth buds are very susceptible to injury. Among adults, the most severe electric accidents occur in linemen who raise their heads or hands and come in contact with a high voltage line (figure 8). A high voltage current will burn; a high amperage current will kill.

Electric burns proper have a yellow-gray appearance and are well demarcated from the normal skin. The burn usually is quite free of pain. In cases of deep electric burns, sloughing and sequestration occur slowly. To save time, it is advisable in some instances to excise the involved area surgically.

Chemical Burns

Burns caused by caustics and acids most frequently are seen in children, students and

industrial workers. In children, the most common cause of chemical burns is contact with or ingestion of lye or laundry bleaches. First aid treatment of acid burns consists of copious washing of the involved area with water until a baking soda paste can be applied. Caustic burns should be copiously flushed with water and vinegar, or a weak solution of acetic acid should be applied. Lye burns are a common cause of accidental blindness. If a child has swallowed lye, vomiting should be induced since the gastric juice will help to neutralize the lye.

Chemical burns of the esophagus usually cause strictures, beginning in about two weeks. A thoracic surgeon should be consulted immediately. Owing to the danger of perforating the esophagus, it is not advisable to pass a tube into the stomach. Orally administered milk and the whites of eggs may be given four or five days after injury.

After removal and neutralization of the causative agent, surface chemical burns should be treated in the routine way with grease compression dressings. Even superficial chemical burns usually will heal slowly, and they remain red for a longer time than heat burns do. Deep burns may be excised or grafted, or allowed to heal by second intention, and a plastic operation may be performed later. Scars of chemical burns are quite prone to be hyperplastic. A keloid may develop in some of them, and subsequent correction may be

FIGURE 8. Burn resulting from high-voltage current that entered the back of the neck of a lineman and came out through the foot, which was grounded. Although electric burns usually are well demarcated, involvement of the subcutaneous tissues frequently extends deep and beyond the limits of the cutaneous burn. Structures such as tendons, bones, joints and blood vessels, which offer resistance, frequently suffer the greatest injury. Injury of these structures may necessitate amputation, as it did in this case. The devitalized tissues of the neck and occipital portion of the scalp were débrided surgically on two occasions. Split grafts from the buttocks were placed on remnants of cervical muscles.

necessary. Chemical burns of the lips of children almost invariably result in microstomia.

Fluorescent light tubes cause a severe chemical burn owing to the presence of beryllium. In almost all cases of this type of burn, except when the burn involves only a small area, excision and repair are necessary. Even tiny burns of this type are extremely indolent.

Irradiation Dermatitis

Some degree of burning of the skin is inevitably associated with all forms of irradiation, since the rays, in order to produce the desired effect on the deeper tissues, must necessarily inflict a certain amount of damage on the skin through which they pass. Fortunately, owing to a better understanding of the effects of irradiation, the use of fractional doses, and emphasis on protective measures for safeguarding the surrounding area, severe skin reactions resulting from irradiation are not encountered as frequently as in the past.

Microscopically, the early changes in cases of irradiation dermatitis are those of inflammation, with proliferation and exfoliation of the epithelial cells. Later, the dermis, including the elastic tissue, hair follicles and glandular elements, undergoes degeneration fol-

FIGURE 9. Hands of physicians who were recipients of small but cumulative doses of irradiation.

lowed by atrophy and sclerosis. Microscopic examination discloses a progressive proliferative endarteritis of the capillaries that is characterized by a diminution in their caliber or by complete obliteration of their lumina. As a result, the tissues that they nourish become ischemic and may undergo ulceration and necrosis.

The late effects of irradiation injury may not appear for 5 or 10 years or more. These effects first are evidenced by telangiectasia, by irregular pigmentation, by dryness, cracking and ulceration of the skin, and usually by moderately severe pain or burning discomfort (figure 9). In some cases, malignant degeneration of the squamous cell type may occur.

The most frequent recipients of irradiation injury are persons who have received irradiation for the removal of congenital port-wine stains, other types of hemangioma or superfluous hair, or for the treatment of acne, eczema, epidermophytosis, pruritus or recurring bursitis. There is a well-known group of professional people—physicians, dentists, veterinarians and x-ray technicians—who often receive cumulative small doses of irradiation. Such doses may be received while a physician, chiefly a general practitioner, reduces fractures under the fluoroscope screen, when his anxiety for the welfare of his patient dulls his regard for his own safety. Prolonged exposure under the fluoroscope screen when searching for a foreign body also is hazardous. The fingers of x-ray technicians and dentists may be burned if they hold the films or plates during the exposure. Faulty calibration of equipment or miscalculation of dosage, distance or filters may result in injury.

Sailor's disease and farmer's skin—The dry, atrophic, telangiectatic changes seen primarily in the skin of farmers in the southern and western parts of the country who have long been exposed to actinic irradiation are similar to those of irradiation dermatitis. They occur primarily in thin-skinned, blond persons with relatively little skin pigment. The advisability of further irradiation for the treatment of this condition should be questioned seriously.

Treatment of irradiation injury—The treatment of the late effects of irradiation injury is surgical. If the condition is associated with severe pain, contraction or ulceration, complete excision is required, and this necessarily entails the sacrifice of a considerable amount of tissue. The defect may be resurfaced with split grafts if the bed is suitable. However, if bones or joints are exposed or if the bed is unsuitable for the reception of free grafts, a flap graft offers the best prospect for success, since it not only carries its own blood supply but also furnishes nutrition to the surrounding tissues.

Atomic burns—The significance of atomic burns will increase as research progresses to transform and harness atomic energy for useful purposes rather than for destruction.

Conclusions

1. Although the present concepts of the treatment of acute burns are modern, they include the time-honored surgical principles of cleanliness, prevention of infection, and early skin grafting.

2. Continued application of these principles will reduce the morbidity and mortality rates in cases of extensive or serious burns.

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The Evolution of Infant Feeding and the Advantages and Disadvantages of Soured Milk Mixtures

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WILBURT C. DAVISON

THE simplified infant feeding of today is the result of a long struggle against dirt, disease, ignorance and prejudice. From the time of the Ptolemies[1-4] to the present century, wet-nursing was the only method by which an infant whose mother could not nurse him had a reasonable chance of survival. Mixtures of milk and honey,[5] barley broth,[6] and pap (bread soaked in water, wine or beer), and direct nursing from goats,[7-9] asses[8] and even wolves (Romulus and Remus) were used from Biblical times, but the mortality rate for artificially fed infants usually was 75 per cent attributable to marasmus, diarrhea, dysentery or tuberculosis.[10-12]

Contaminated and filthy milk from infected cows was the chief cause of the death of these infants. Hartley pointed this out in his book on milk in 1842,[13] 50 years before the medical profession discovered that clean milk from healthy cows was commercially possible. Starting in 1890 with the tuberculin testing of cattle and in 1892 with the Certified Milk Association, followed by pasteurization in 1895, the health standards of milk[14-16] were raised so that now, under the U.S.P.H.S. Standard Milk Ordinance,[17] most dairies qualify for Grade A rating.

After contaminated and infected milk disappeared or became less common, so that most of the artificially fed infants survived, the so-called scientific era of infant feeding started

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with milk analysis by Liebig in 1865, and especially with Biedert's belief in 1869 that cow's milk should be diluted three times because it contains three times as much protein as woman's milk.[18,19] The "percentage" argument then began.[20] The fat,[21,22] carbohydrate and whey[23] content of cow's milk and high starch diets *(Mehlnährschaden)* also were blamed for some failures in infant feeding.

Most of the efforts to modify cow's milk in this so-called scientific era were based on four premises: (1) that children did not thrive on cow's milk as well as they did on woman's milk, (2) that the difference in the chemical composition of woman's milk and cow's milk was an important factor, especially Biedert's idea[18,19] that the protein of cow's milk caused indigestion, (3) that infants had a weak digestion and were so physiologically different from adults that they could be fed only dilute mixtures, and (4) that, if a child vomited, had diarrhea and did not gain, only his diet was at fault, and it alone should be changed.[24,25] It certainly was true that children did not thrive on the cow's milk of a generation ago. The logical French used the milk of asses and mares, which has a composition similar to that of woman's milk[26] (table 1). Perhaps the most useful contribution of this epoch was Huebner's calculation of the caloric content of infant diets.[36]

TABLE 1

PERCENTAGE COMPOSITION OF MILK OF VARIOUS ANIMALS[14-16,27-35]

ANIMAL	PROTEIN	CARBOHYDRATE	FAT
Woman	1.6	6	4
Ass	2	6	2
Camel	4	6	3
Cat	9.5	5	3
Chimpanzee	0.6	7.2	2.3
Cow	3.5	5	4
Dog	7.1	3	10
Elephant	3	9	20
Goat	4.3	5	8
Guinea pig	5	2	7
Mare	2	7	1
Pig	5.9	3	7
Rabbit	10	2	17
Rat	12	3	15
Reindeer	10	2	17
Sheep	6.5	4	9
Whale	?	?	44

The number and variety of milk mixtures devised for infant feeding were legion,[37-43] e.g., the dilute feedings of Czerny of Strasbourg,[21,22] Holt of New York and Howland of Baltimore; the high and low fat mixtures of Rotch[20] and Morse of Boston; the cream mixtures of Winters of New York; the *Buttermehlnährung* of Kleinschmidt of Germany; the *Eiweissmilch* of Finkelstein of Berlin;[23] soft curd milk;[44-46] acidophilus milk;[47] the lactic acid evaporated milk of Marriott of St. Louis;[37-43] the hydrochloric acid mixtures of Faber of San Francisco[48] and Scheer of Germany; and the citric acid,[49-52] lemon juice,[53] vinegar,[54,55] acetic acid and other acid mixtures.[56-61] In fact, infant feeding became too complicated for medical students and physicians, and it was a great help to the public when the food manufacturers simplified the problem.

At present, there are more than 125 proprietary infant foods. Many of these are listed in table 2 and are illustrated in the frontispiece of Myer's book.[62] The cost of these foods ranges from 33 to 62 cents per 1000 calories (table 3). These milk mixtures and proprietary products are of two kinds: (1) those modified for normal infants, usually to resemble the fat and protein content of woman's milk, and (2) other products such as soybean preparations,[63,64] amino acid mixtures and low sodium milk, which serve special and very useful purposes.

There are three reasons for this multiplicity of infant diets.[24,25,27,45e,58,65] The first of these is the unclear teaching in most medical schools. Few graduates, even pediatricians, acquire much sound knowledge of infant feeding while in medical schools or in residencies. There are so many conflicting views on the subject, most of them erroneous, that it is no wonder that students and physicians are so confused that they rely on the directions on the can of a commercial product because these at least are simple and clear. The second reason is that many physicians do not adequately explain the preparation of milk mixtures to mothers. Too, some mothers will not follow directions,

simple though these are.* The third reason is the former rivalry of the heads of various clinics on this subject. A Hopkins' graduate who served as assistant resident on the old Boston Floating Hospital had to swallow Morse's jibes at Howland's dilute formulas. Howland, on the other hand, had an equally low opinion of Morse's Harvard high and low fat percentage mixtures.

It seems foolish now for Howland to have required that his assistants should know calculus and carry a slide rule as standard equipment in order to calculate meticulously the caloric content of the infant feedings consisting of dilutions of sweet milk, since it was obvious to every intern that such calculations were inaccurate because the original fat content of the milk with which they were made varied from day to day and from dairy to dairy. Furthermore, when a level tablespoonful of sugar was measured with tablespoons obtained from several homes, its weight was found to vary from 7 to 16 gm.[67] Certainly, the variations in the percentage composition of breast milk in different women, and at different times in the nursing period as well as during the day from a single breast[68,69] are as great as those in the milk of Holstein, Guernsey and Jersey cows and various mixtures of the milk of these cows (table 4). However, these differences in breast milk do not have any obvious effect on infants.

A tremendous advance in infant feeding was made when physicians began feeding on the basis of the reactions of the child as a whole and ceased to be guided entirely by the stools.[70] The old reliance on the appearance of the stools was absolutely pernicious and the fallacy was brought to light coincidentally by Finkelstein,[23] Marriott[37-43] and Pirquet.

Two papers by Powers[24,25] probably had the greatest influence in breaking up the old ideas. He showed that, on the basis of the calories of fat, carbohydrate and protein, all foods used in the feeding of infants probably were the same. They were merely milk with different additions of carbohydrate or reductions in fat, but the changes in the carbohydrate and fat were really inconsequential since the foods remained essentially cow's milk.[70] Another advance was the demonstration that a liberal supply of fluid was essential and that water should be offered at the end of each nursing (to keep the mouth clean) and at intervals between feedings.

Simplification and safety in infant feeding were largely attributable to Marriott[37-43] who cut the Gordian knot of the confusion by saying that, because he and everyone else knew so little of the relative merits of these various mixtures, he selected one safe and digestible infant food, namely, soured whole milk or whole buttermilk (not the usual skimmed or fat-free commercial buttermilk). Marriott's

**Directions for preparing lactic acid evaporated milk (LAEM) in the home*—The mixture consists of the contents of a 13 oz. can of unsweetened evaporated whole milk, 17 oz. of water, 2 tablespoonfuls of sugar and 1.5 *teaspoonfuls* of lactic acid. An ounce of this mixture contains 23 calories. It can be used for all normal infants who are less than eight months old. If it is used for older children, the sugar should be omitted. The omission of the sugar will reduce the number of calories to 20 per ounce.

Scald with boiling water a clean quart jar or milk bottle and an empty, clean, 13 oz. evaporated milk can. Fill the empty milk can with water, and pour the water into the quart jar or milk bottle. Add 2 level standard tablespoonfuls of ordinary table sugar and 1.5 standard *teaspoonfuls* of lactic acid to this water. As soon as the sugar has dissolved, cool the sugar and lactic acid solution. (Chilling the solution facilitates mixing and produces a smoother curd.) Open a 13 oz. can of unsweetened evaporated whole milk, and, with continuous gentle shaking, pour the contents of the can slowly into the quart jar or milk bottle containing the *cold* sugar and lactic acid solution. (Do not pour the solution into the milk.) Finally, fill the quart jar or bottle nearly to the top with cold water, and reshake to make the mixture smooth. The mixture should not be boiled or pasteurized since this will cause it to curdle. Refrigeration is unnecessary.[66] Lastly it should be poured into sterile nursing bottles in the amounts required for each feeding.

If the water supply is bad or is well or pump water, it should be boiled and cooled before it is used. A level standard tablespoon holds 12 gm. of sugar. A level standard teaspoon holds 5 ml. of lactic acid. Tablespoons obtained from several homes held from 7 to 16 gm. of sugar. Home teaspoons held from 3 to 6.3 ml. of lactic acid.[67] Ordinary table sugar is as satisfactory as KARO® syrup or any other sugar.

It is safer and probably as efficacious to substitute 3 standard tablespoonfuls of ordinary apple cider vinegar for the 1.5 teaspoonfuls of lactic acid.[55]

Warning—Lactic acid is a deadly corrosive poison. (One ounce of lactic acid U.S.P. can be fatal.) It never should be handled or measured carelessly or left within the reach of children.

TABLE 2

SOME AMERICAN AND BRITISH COMMERCIAL INFANT FOODS

ALACTA®	Benger's food*	Cow and Gate tropical*	Evaporated goat's milk
Allenbury's Nos. 1 and 2*	Beurlac*	Cow and Gate humanized*	Farex*
Allenbury's cereal*	BIOLAC®	Cow and Gate malted food*	Farine Lactee (Nestlé)
Allenbury's malted food No. 3*	BREMIL®	DALACTUM®	Ferrolac full cream*
Allenbury's sweet whey*	Brestol*	DALE® dehydrated goat's milk (Cutter)	Ferrolac fat modified*
Allergilac*	Calcilac*	Daltose*	First Swiss*
Almata*	CASEC®	DEXTRI-MALTOSE® and whole milk	FORMULAC®
Ambrosia full cream*	Casumen*	DEXTROGEN®	Frailac*
Ambrosia half cream*	Casumen milk protein food*	Diploma*	Full weight*
Ambrosia with added iron*	Casydrol*	Dorsella full cream*	Geego full cream*
Ambrosia humanized*	Cerex*	Dorsella with added iron*	Geego half cream*
Anglo-Swiss*	Chapman's chole flour*	Dorsella humanized*	Geego separated*
AROBON®	Cheltine malted milk*	DRYCO®	Glaxo*
Baker's modified milk, liquid	Cow and Gate full cream*	Eledon*	New Glaxo*
Baker's modified milk, powdered	Cow and Gate half cream*	ENZYLAC®	Hemolac*
Bananina*	Cow and Gate special half cream*	Evaporated cow's milk	HI-PRO®
	Cow and Gate separated*		Hollandia*
			Horlick's malted milk

*British product

original reason for using soured milk was that it diminished the work of digestion. When buttermilk enters the stomach it already is at the desired pH whereas sweet milk has to be reduced to the optimal pH by the secretion of hydrochloric acid. Later, he suggested that its bactericidal action made it safer,[37-43] as Rothey[71] subsequently demonstrated.

Buttermilk has had an interesting history. It was first recommended as an infant food by Rosén von Rosenstein[72] in 1776, but its use was limited until 1865[73,74] when the thrifty Hollanders who sold butter to Britain and Germany noticed that they could raise excellent hogs and babies by feeding them the surplus buttermilk. In Germany, fresh and dried buttermilk soon became known as *Hollandische Nährung* following the publication of a paper by de Mattos in 1902.[75,76] Its use was introduced in France about 1907 and in the United States about 1913, probably by the late Alfred F. Hess.[53]

The use of buttermilk became so popular that the supply was inadequate unless hogs were deprived of it. Marriott and Cooke, therefore, introduced cultured whole buttermilk.[37-43] Several laboratories then went into the business of supplying homes, hospitals and dairies with "milk starters" that consisted of a concentrated culture of *Lactobacillus bulgaricus, Streptococcus lactis* or *Lactobacillus acidophilus*. When fresh or pasteurized whole milk was inoculated with this milk starter and incubated overnight, a smooth "buttermilk" was produced.

Marriott and Davidson next found that the main difference between cultured whole buttermilk and sweet milk was that the former contained 0.75 per cent of lactic acid. They also found that equally good buttermilk could be made by adding this amount of lactic acid to whole sweet milk.[37-43] Later, Marriott and his group at the St. Louis Children's Hospital started using lactic acid evaporated milk (LAEM), which has numerous advantages. Recent experiments by Seymour, Taylor and Welsh[55] have demonstrated that the substitution of apple cider vinegar for lactic acid retains all of the virtues of lactic acid milk and, in addition, avoids the danger of poisoning from undiluted lactic acid. Furthermore, vinegar is much cheaper than lactic acid and can be obtained at any grocery. Citric acid (lemon juice) has been used extensively by Jeans.[49-52] It has the advantage over lactic acid of not being poisonous, but it has the disadvantage of not being as bactericidal.[71]

In an earnest effort to learn something about infant feeding and diarrhea, one of us (W. C. D.) spent the summers of 1919 to 1929

TABLE 2 *(Continued)*

SOME AMERICAN AND BRITISH COMMERCIAL INFANT FOODS

HYPO-ALLERGIC® milk	Mellin's food	National dried milk*	Robinson's patent barley*
Ideal milk*	Mellin's Lacto	National dried milk, half cream*	Rose*
KLIM®	Milkmaid*	NUTRAMIGEN®	Savory and Moore's food*
Lacidac full cream*	Miriam's food*	OLAC®	Scott's Midlothian oat food*
Lacidac half cream*	Modilac*	Ostermilk, Nos. 1 and 2*	Secway*
Lacidac separated*	Moseley's food*	PELAGRON®	SIMILAC®
LACTOGEN®	Merrell-Soule powdered lactic acid milk	Peptalac*	Sister Laura's food*
Lacquim*	Merrell-Soule powdered lactic acid milk, skimmed	Prenatalac*	SMA® powder
LACTUM®	Merrell-Soule skimmed milk	Prolac*	SMA® protein milk, acidulated
Libby's	Merrell-Soule powdered protein milk	Pronutrin*	SOBEE® and Dextri-Maltose
LONALAC®	MULL-SOY®	Prosol*	Sprulac*
Mead's powdered lactic acid milk No. 1 (with Dextri-Maltose)	Meyenberg evaporated goat milk	Protosol*	Trufood*
Mead's powdered lactic acid milk No. 2 (plain)	Neave's food*	PROTENUM®	Trufood humanized*
Mead's powdered protein milk with Dextri-Maltose	Nestlé's evaporated milk	PROTOLYSATE®	VARAMEL®
		Recolac*	Veguva, Nos. 1 and 2*
		Ridge's food*	Viking*
		Robinson's patent groats*	Vitasoy*

visiting the pediatric clinics from Baltimore to Boston and from San Francisco to Budapest. The infants in these various cities apparently thrived equally well on any mixture provided it contained enough calories, protein, calcium, vitamins and fluid,[49-52,77] and provided that it was sterile. This confirms Marriott's belief in any safe and digestible mixture.[37-43]

Forty pediatric friends in this country and abroad and 13 manufacturers of infant food who were asked for suggestions agreed that there are at least seven requirements for a satisfactory feeding mixture: (1) digestibility; (2) adequacy of fat, carbohydrate, protein, calcium, fluid calories, etc.; (3) safety of source; (4) uniformity; (5) universal availability; (6) simplicity and (7) cheapness. They agreed that these requirements could be met by evaporated milk, sugar and water,[37-43,45f,54,78-85] and by several other simple mixtures[45e,56,57] of fluid or powdered milk just as well as they could be by more expensive preparations, except that evaporated milk is difficult to obtain in Great Britain and its cost in Central America is higher than that of fluid or powdered milk.

What our pediatric colleagues did not endorse was the advisability, let alone the necessity, of a bactericidal feeding. In the South and Middle West, lactic or citric acid often was added to infant feedings, but on the Eastern Seaboard, no credence was given to Marriott's and our belief that acid milk was superior to sweet milk mixtures.

We, therefore, felt that the virtues of soured milk merited a defense. It is agreed that as far as weight gain and digestion are concerned, sweet milk and acid milk mixtures of similar composition are interchangeable. The value of acid milk is *solely* in its bactericidal activity,[37-43,45f,55,71,86] which is especially important for poor people in rural areas who do not have refrigerators.[66] Lactic acid milk will prevent intestinal infections,[85-87] and will remain sterile for three days at room temperature.[66] The widespread use of lactic acid milk in North Carolina has undoubtedly been an important factor in the reduction in the incidence of dysentery and diarrhea in this locality.[86] Furthermore, as far as could be learned, epidemics of infantile diarrhea in northern hospitals have occurred only in those institutions in which acid milk has not been used. Dysentery in infants and adult dysentery carriers are still hospital problems, and a bactericidal milk is advantageous.

It is granted that terminal sterilization and pressure sterilization are necessary if sweet milk mixtures are used.[88-94] However, a generation ago, Wilkins[95] proved that the boiling

TABLE 3

RELATIVE CONTENT AND COST OF SOME FOODS FOR DAILY ROUTINE FEEDING OF NORMAL INFANTS*

	VOLUME *(milliliters)*	PROTEIN *(grams)*	CARBOHYDRATE *(grams)*	FAT *(grams)*	CALCIUM *(grams)*	RETAIL COST *(cents)*
Breast milk, human	1400	22.4	84.0	56.0	0.5	210.0†
Cow's milk	1400	49.0	70.0	56.0	1.7	35.0
Lactic acid evaporated milk	950	33.8	120.8	38.6	1.1	19.0
Commercial products‡						
1	1480	34.0	107.0	50.0	1.3	40.0
2	1480	44.1	116.2	44.1	1.6	44.6
3	1480	22.8	106.4	49.7	1.2	46.4
4	1852	76.2	109.5	28.6	2.4	46.7
5	1646	52.3	74.4	56.8	1.9	42.7
6	2690	100.8	143.0	2.8	3.6	33.4
7	1558	53.0	65.0	56.0	1.9	43.2
8	2690	101.8	144.4	2.8	3.6	48.6
9	1560	26.9	103.6	52.5	1.2	40.0
10	1532	39.5	119.0	41.3	1.5	55.0
11	1845	50.8	156.8	19.0	1.8	49.0
12	1429	49.7	112.9	40.3	1.5	51.0
13	1716	52.8	151.4	19.2	1.9	47.0
14	1662	42.4	125.9	47.3	1.5	62.0
15	1479	41.2	132.4	40.4	1.7	52.0
16	1479	42.8	174.1	21.8	1.7	52.0
17	1500	31.2	102.6	48.1	1.2	41.0
18	1500	36.0	110.4	37.8	1.2	35.8
19	1400	39.6	107.3	41.7	1.5	40.8
20	1480	22.2	103.5	51.8	0.7	43.1
21	1350	49.0	64.9	57.0	1.4	42.0
22	1480	38.0	110.0	46.0	1.4	42.0

*When these foods are prepared and ready to be fed to an infant, the stated quantity of each will contain approximately 1000 calories.

†At breast-milk stations.

‡Some of these products contain added vitamins, iron and other minerals. In some of the products, nonbovine fats and/or proteins have been substituted for the fats and/or proteins of cow's milk. Cocoa or other flavoring has been added to some of the products.

of milk mixtures in their final bottles only slightly reduced the incidence of diarrhea and dysentery, and Scheuer[85] demonstrated that the boiling of milk was not nearly as effective in this respect as was lactic acid evaporated milk, which cannot be boiled or pasteurized because it will curdle. Furthermore, if lactic acid milk is used, the milk preparation layout in a hospital is greatly simplified and the operating costs are reduced.[96] The reduction in the number of fermentative organisms in the upper part of the intestine of infants fed lactic acid milk also reduces the possibility of noninfectious summer diarrhea as well as of dysentery.[87]

Twenty-five years ago, a review of the various methods of feeding full-term and premature infants, both those who were normal and those who were ill, who could not be breast fed, led to the use of lactic acid evaporated milk at the Duke Hospital.

Advantages of Lactic Acid Milk

Digestibility—Infants thrive on lactic acid milk at least as well as they do on breast milk.

Adequacy—Lactic acid evaporated milk contains sufficient protein and calcium, but, as in all cases in which artificial feeding is used, every child who is less than three years old should be given vitamins C and D.

Safety—Even though the original milk might not always have been Grade A, the evaporation process removes the risk of brucellosis, tuberculosis, typhoid fever and

other diseases which can be spread through dairies.[59-61] The modification of the milk proteins by the evaporation process and acidification also is helpful for allergic infants.[97] The addition of lactic acid prevents the growth of organisms that cause dysentery and species of *Salmonella* with which flies or fingers may contaminate milk.[36-42, 71] Sweet milk and powdered milk mixtures (except powdered lactic acid milk), even when boiled in the nursing bottle or final container, can be infected by the mother's or nurse's hands while they are attaching the nipple or handling the bottle. Furthermore, methemoglobinemia due to nitrate-containing well water does not occur in infants fed lactic acid milk mixtures. This is a valuable asset in rural areas.*

Uniformity—The percentage composition and quality of evaporated milk are much more constant than those of dairy milk.

Universal availability—As indicated previously, lactic acid evaporated milk can easily be prepared at home without elaborate equipment. In hospitals, the time required in the milk room is only one-third of that required in institutions in which sweet milk formulas are used.[88-91]

Cheapness—One of the main reasons for this paper is to encourage physicians to use lactic acid evaporated milk not only because of the advantages that have been mentioned but also because it is the cheapest infant formula. The cost of lactic acid evaporated milk is half that of dairy milk or of many other infant foods (table 3).

Disadvantages of Lactic Acid Milk

Concentrated solutions of lactic acid are poisonous. Death has occurred in cases in which too much lactic acid has been used in a feeding mixture, in cases in which it has been swallowed by children, in cases in which it has been used for gavage, and even in a case in which lactic acid U.S.P. (85 per cent) has been used as an enema.[99-101] However, even the risk of lactic acid poisoning, bad though it is, is less than the risk of serious dysentery in large cities as well as in the country, and especially in children's hospitals[102] and foundling homes.[85] Using vinegar instead of lactic acid overcomes this difficulty.[55]

*The lactic acid is bactericidal for the intestinal bacteria that convert the nitrates in the ingested well water to the nitrites that cause methemoglobinemia.[18]

TABLE 4

PERCENTAGE COMPOSITION OF MILK OF FIVE BREEDS OF COWS[11-16, 28-35]

BREED	PROTEIN	CARBOHYDRATE	FAT
Guernsey	4.02	4.91	5.19
Jersey	3.86	4.94	5.18
Ayrshire	3.58	4.69	4.14
Holstein	3.42	4.86	3.55
Shorthorn	3.32	4.89	3.63

A further disadvantage of lactic acid or vinegar evaporated milk is its taste. Some infants, especially those who previously have been fed with very sweet mixtures, dislike lactic acid evaporated milk, but this difficulty always can be overcome if the physician and the mothers will cooperate. In fact, many children prefer it to sweet milk after they have become accustomed to it. The addition of flavoring agents, such as chocolate syrup, improves the taste of soured evaporated milk, especially for older children and adults.

Vitamin supplements restore any slight loss of vitamins in processing and guarantee a uniform vitamin A, C and D content which may vary in milk from different dairies and from different cows, depending on their diet and breed. Lactic acid and vinegar do not have any effect on the ascorbic acid content of milk.[103] The concentration of lead in canned milk is of no practical importance.

The hypocalcemia and hyperphosphatemia that are said to have occurred in infants who have been fed evaporated milk[104, 105] might possibly have been avoided if lactic acid or vinegar had been added to the milk. Infantile tetany has not occurred in any of the full-term or premature infants who have been fed lactic acid evaporated milk at the Duke Hospital. It is possible that the increased acidity mobilized the calcium by increasing its absorption, ionization and utilization. As neonatal electrolytic homeostasis is reached within 4 to 24 hours after birth,[106] there does not seem to be any biochemical reason why the

use of lactic acid evaporated milk cannot be started at the end of the first 24 hours.

Infants who are fed lactic acid evaporated milk occasionally have red buttocks, which apparently are not significant.

Conclusions

1. All infants should be breast fed, not because human milk is necessarily better than other infant feeding mixtures but because it creates a sense of security and is of psychologic advantage to the infants.

2. Just as surgeons are utilizing the prophylactic advantages of antibiotics such as penicillin, ACHROMYCIN®, streptomycin and TERRAMYCIN®, pediatricians should combine the bactericidal effect of lactic acid with that of other measures to provide infants with a safe feeding that will prevent diarrhea. Lactic acid evaporated milk may not always be necessary, but, like fire insurance, it is good to have in time of need.

3. On the basis of its digestibility, adequacy, safety of source, safety of home preparation, prevention of diarrhea and dysentery, universal availability, simplicity of preparation, lowered antigenicity, and cheapness, lactic acid evaporated milk (LAEM) or vinegar evaporated milk (VEM) is the best infant feeding at present.

Because of space limitations, the bibliography has been omitted here but a complete list of references is available on request to the Editorial Department of POSTGRADUATE MEDICINE and in the authors' reprints.

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Emergencies in the Newborn Period

In the last 30 years, the death rate for the first year of life has dropped about 10 per cent. During this period, the death rate for the first month of life has dropped only about 1 per cent. Among the common causes of death during the newborn period are abnormal pulmonary ventilation, including atelectasis and hyaline membrane disease; congenital anomalies; infections, and blood dyscrasias. Newer concepts in managing these conditions will be discussed, as well as a number of the less serious but irritating neonatal "headaches."

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Clinical Significance of a Sliding Hiatus Hernia

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A SLIDING hiatus hernia of the stomach through the diaphragm is defined as a mass movement upward of the lower part of the esophagus and cardia into the chest through the esophageal hiatus. In this discussion, a congenital short esophagus and a sliding hernia are considered the same. The clinical manifestations of this condition depend on two physiologic disturbances. The first is failure of co-ordinated muscular activity of the esophagus resulting in intermittent episodes of aphagia. This is not related to inflammation and spasm secondary to reflux of stomach juices. The second includes changes associated with reflux of digestive juices into the esophagus through a poorly functioning sphincter. Both of these symptom complexes follow a distortion of the esophagogastric junction from the sliding hiatus hernia.

Fifty-one patients with sliding hiatus hernia have been seen in the thoracic surgical division of Duke Hospital in the last four years. Some of the experience with these patients is outlined.

The physiology of the esophagogastric area of the intestinal tract is poorly understood. Some observers have denied the presence of a smooth muscle sphincter in the area, and have postulated that it is the striated muscle of the diaphragmatic crura that acts as the sphincter.[1] There is a protective mechanism against the reflux of digestive juices at the cardia, and, as is true of continuously functioning sphincters elsewhere, it must be composed of smooth muscle. It is possible that the striated muscle of the crura of the diaphragm may act as a safety mechanism during periods of increased abdominal pressure, but it is not logical to think it can maintain constant contraction at all times. Studies of Lerche[2] indicate that there exists a smooth muscle mechanism at the esophagogastric junction that serves as

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a sphincter. The transit of a bolus of food through the esophagus to the stomach may elicit a series of very complex co-ordinated muscular movements. Since the sliding hiatus hernia is the only demonstrable abnormality in patients who have either episodic aphagia or reflux esophagitis, one must assume that it is the distortion of the anatomic arrangement at the esophagogastric junction that causes this physiologic disturbance.

When normal gastric juice is allowed to reflux into the esophagus, severe corrosive changes occur. The more potent the digestive ferments, the greater the erosion; thus, the severe changes noted in duodenal ulcer patients. The longer the contact, the greater the damage, which explains why so much damage to the esophagus comes at night. In addition to gastric juices, the esophagus is very vulnerable to digestive ferments of the small intestine. These points are stressed because operations that only diminish, but do not abolish, the gastric digestive substances, and those that bypass the stomach by esophagojejunostomy are not likely to succeed.

Reflux esophagitis may appear only as occasional episodes of heartburn, and associated with this there may be mild esophageal inflammation. Difficulty in swallowing, which was present in 29 of our 51 patients, comes on sometimes from spasm, but it can result from ulceration and fibrosis of the esophagus. Regurgitation of gastric content, particularly when the patient strains or is in the recumbent position, was noted in 27 of our 51 cases. The pain from inflammation of the esophagus may be localized to the epigastrium or may be referred to the mandible, shoulder or the thoracic vertebrae. Finally, the inflammation and erosion may result in bleeding, and in 13 of our 51 cases this was the presenting complaint. It is surprising how minor the esophageal erosion was in nearly all of these 13 cases. In one case, the patient had no symptoms other than hemorrhage. In four cases, bleeding was massive.

In 11 of our 51 cases, definite fibrous stenosis of the esophagus developed. In five cases, this followed vomiting after operation or during pregnancy. Four of these patients had associated duodenal ulcers. The degree of stenosis is very difficult to ascertain. The strictures respond unusually well to only a few dilatations, indicating that secondary spasm may be responsible for much of the narrowing shown by roentgenograms.

In 22 of our 51 patients, episodic aphagia was noted. It was quite striking that esophagoscopy revealed that six did not have corrosive esophagitis. Episodic aphagia is defined as sudden limited attacks of complete inability to swallow. This may subside in a few moments, and then swallowing function returns to normal. It may persist, and the patient will sometimes have to regurgitate his food before relief is obtained. In other instances, the aphagia may continue for several hours, the esophagogastric junction will then relax, and swallowing function will then be normal. Since this symptom may be present without esophagitis, it is thought to represent disorganization of the muscular co-ordination of the esophagus and the sphincter. It should be pointed out that both episodic aphagia and reflux esophagitis can be present in the same patient.

In 8 of our 51 cases of hiatus hernia, there was an associated duodenal ulcer. When there is sphincter incompetence at the cardia of the stomach, the continuous secretion of high quality stomach juices will result in severe esophagitis.

Diagnosis

The diagnosis in cases of suspected hiatus hernia is dependent for the most part on roentgenologic examination and esophagoscopy. There were, in our 51 cases, four in which the lesion could not be demonstrated roentgenologically on the first examination, but esophagoscopy disclosed the hernia. This was later confirmed by further radiologic examinations. On esophagoscopy, the inflammation of the mucosa may be superficial and localized, but it can extend to the aortic arch. The patulous esophagogastric junction is the most striking finding and has been present in all instances. In severe examples, the esophagus may be shortened by actual measurement. In our experience, esophagoscopy is more accu-

rate than roentgenologic examination in the diagnosis of a sliding hiatus hernia. X-ray studies should be made with the patient in the head-down position. Other abnormalities should be carefully sought, because duodenal or gastric ulcer may mimic reflux esophagitis.

Stool examination for blood should be included. In some instances, the discomfort of the hernia may be referred to the precordium and resemble a coronary insufficiency, so that careful evaluation of the cardiac status is necessary. In addition to studies of the gastrointestinal tract, the biliary system should be investigated.

The complications of hiatus hernia that are severe are the consequence of reflux esophagitis. These may be severe bleeding, or stenosis from fibrosis, and ulceration. Aspiration of regurgitated gastric contents into the lung occurs, and after a long period of time may result in irreversible pulmonary changes.

Treatment

In treatment of patients with a sliding hiatus hernia, it is necessary to decide whether or not the hernia is the cause of symptoms. Episodic aphagia is unmistakable. When there is reflux of stomach contents into the pharynx following recumbency, there is usually little doubt about the significance of the hernia. In certain instances, particularly if it is impossible to separate the symptoms of reflux esophagitis from those of some functional disturbance, gallbladder disease or cardiac pain, esophagoscopy is useful. The demonstration of esophagitis will usually settle the matter of the hernia's significance. It is very likely that most of the sliding hiatus hernias are the cause of symptoms.

The keystone of the conservative management of patients who have reflux esophagitis is based on keeping the stomach as empty as possible when the patient is recumbent. Patients are instructed to remain upright for at least three hours after meals. Night reflux is prevented by elevation of the head of the bed. Painful swallowing can be relieved by administering 5 cc. of 1 per cent solution of procaine hydrochloride before meals. During exacerbations, only soft foods should be given.

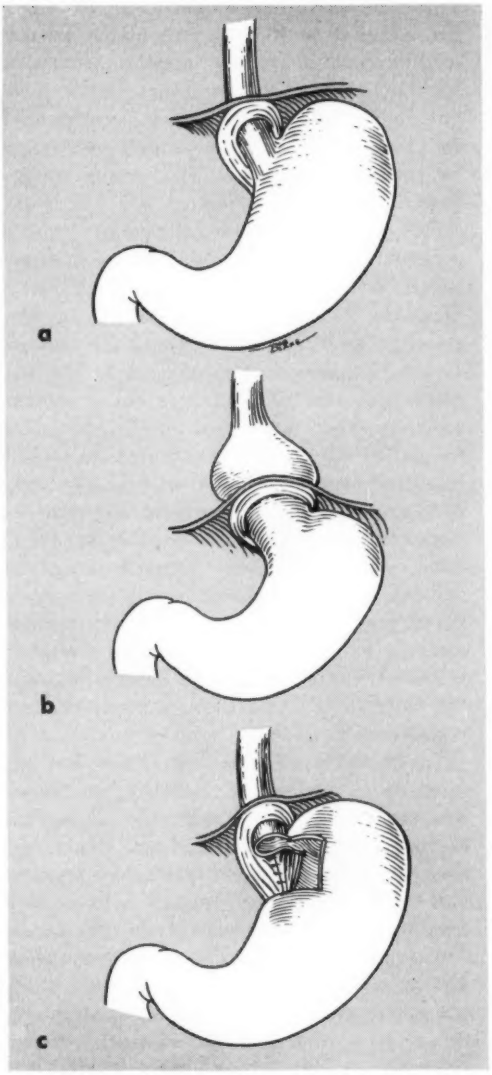

FIGURE 1a. Normal relationship of esophagus, stomach and diaphragmatic crura.

b. Sliding hiatus hernia with widened diaphragmatic crura and esophagogastric junction high above the diaphragm. It is this anatomic situation that results in symptoms of a hiatus hernia.

c. A very simple procedure advocated by Allison for repair of a sliding hiatus hernia. The stomach is reduced and the esophagogastric junction realigned, thereby allowing the sphincter to regain its function. In addition to repair of the hiatus as shown here, the phrenicoesophageal membrane is fixed to the undersurface of the diaphragm.

The most important single thing to remember is not to treat these patients by frequent feedings, as though they had a duodenal ulcer, for they do not have abnormal gastric juices, nor do they secrete gastric juice continuously. In 25 of our 51 cases, the patients were treated by conservative means. The results in these cases have been only fair.

In 26 cases we found that operation was indicated, frequently because medical treatment failed. With increasing experience, other indications were suggested. History of long-standing gastric reflux indicates the need for surgical intervention, for danger of bleeding, ulceration, stricture and pulmonary contamination is great. Significant bleeding should be treated by surgical intervention. Patients with duodenal ulcers associated with hiatus hernia need prompt surgical treatment, for complications are much more likely to occur in patients with combined lesions. Episodic dysphagia not associated with other symptoms may demand treatment, since conservative management is very unsatisfactory. This complaint may be very troublesome and embarrassing as the patients often have to interrupt meals to regurgitate their food.

In 21 cases in which operation was performed, the procedure described by Allison[3] was used. In this operation, the sliding hiatus hernia is reduced below the diaphragm, the widened esophageal hiatus is repaired, and the divided esophagophrenic ligament is fixed to the undersurface of the diaphragm. This procedure is done best through the chest. This operation accomplishes only one thing. It restores the distorted esophagogastric junction to its normal position (figure 1). The attainment of this simple objective prevents malfunctioning of the sphincter. In 20 of the 21 cases having the benefit of this operation, the patients were relieved of their symptoms. There was only one recurrence. Follow-up has varied from one to four years.

In cases of complicated hernia in which there is bleeding, repair of the hernia will control the hemorrhage. When there are an ulcer and a stricture, conservative operation is mandatory. Resection of the cardia and lower part of the esophagus only leads to the very situation that causes the trouble. It has been our policy to reduce the sliding hiatus hernia and to follow this with esophageal dilatations.

Dilatations of the esophagus, carefully done, may be most useful in instances of stricture formation and episodic aphagia. Patients who have only the latter complaint learn to administer their own dilatations. In three cases in which a stricture from healing esophagitis has developed after hernia repair, dilatations have opened the esophagus and preserved some sphincter function. In four cases, dilatations plus medical management have controlled symptoms. In the latter cases, operation was contraindicated for other reasons.

Resection of the lower part of the esophagus should be performed only as a last resort. In two of five cases in which this was done, esophagitis and stenosis recurred. In one case, the patient died in the postoperative period. This operation is contraindicated unless there has been a long trial with conservative management consisting of dietary control and esophageal dilatations. Since the esophagus is very sensitive to even poor quality digestive juices, it is not advocated to resect the stomach or to do a vagotomy and gastroenterostomy. When there are a duodenal ulcer and an esophageal ulcer with hiatus hernia, treatment of both as separate entities is advocated.

Summary

A sliding hiatus hernia may cause sudden episodes of aphagia from failure of co-ordinated sphincter action, and reflux esophagitis from loss of the cardiac sphincter function. Simple repositioning of the stomach and esophagus to their normal positions alleviates these symptoms.

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Palliative Treatment of the Constitutionally Inadequate Patient

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THE topic of this paper is actually "Coping with crocks." However, to the end of more sophistication, the title has been given as indicated above.

The human subject is most often, but not always, a female between the ages of 20 and 50. Her chief complaints are multiple and usually have existed as long as she can remember. She is obviously in no acute distress but just as obviously not happy.

Head—Headaches have been killing her all her life. These are characteristically in the back of the head, often with drawing over the scalp. Although the pain is blinding, an aspirin will give relief for just a few minutes. Teeth and tonsils usually have been removed due to "source of infection." Sometimes spots before the eyes are disturbing and tinted glasses may be worn. Weird noises in the head are not infrequent. The throat is a site of choking as if a band were around the throat or something in the throat will not go down. She has consulted at least three E.N.T. specialists who could find nothing wrong. She has lost confidence in them.

Cardiac—The patient's heart races and stops and scares her to death. She smothers at bedtime, most especially when her husband is at home. She has pain over her heart which may at times extend over her entire left side including the left side of her face. She almost always complains of low blood pressure. She has had negative electrocardiograms and has lost confidence in heart doctors.

Respiratory—She has had no chronic cough but she has bouts of terrible coughing, usually when her husband has taken a drink. At least on one occasion, she has spat up a lot of red blood—in fact, a little red streak on some sputum which may have been cough syrup. After all, chest plates have been negative repeatedly. She emphatically believes chest x-rays do not show everything.

Gastrointestinal—Digestion is poor. Bloating is common, usually after having to heave for her breath. Heartburn is frequent. She

either cannot eat a bite or she cannot stop eating. She has to take something for her bowels. She has hard stools or her movements are frequent and have some slime in them. Pain in the abdomen is always all over, never at a specific point where one finger may be pointed. Complete gastrointestinal series have been negative. She feels that the gastroenterologists did not know what they were doing. She has lost confidence in stomach specialists.

Genitourinary—Frequency is common, not associated with dysuria, hematuria or pyuria. Repeated urinalyses are negative. Cystoscopic examinations with retrograde pyelograms and intravenous pyelograms have been negative. She is disappointed in the results of the tests, the bills and urologists.

Skeletal—Low back pain is always present—all over the back, even extending to the back of the neck. Usually an orthopedist has almost killed her by putting her on a hard old bed. She has lost confidence in orthopedists.

Menses—Periods are always extremely painful, "just like mamma's," that is, if the uterus has not been removed. The amount is never normal, nor are periods regular. "Bearing-down feeling down there is going to drive me crazy." Intercourse is extremely painful. She would rather die than have another baby. She has had "change of life" as long as she can remember.

Allergy—She has allergic itching "down there," the causative agent never determined. She has allergic whelps when she gets excited. She believes generalized itching at times is due to allergy. Often, meats, vegetables and fruits make "the allergic condition" of her stomach worse. Skin tests and elimination diets have been of no avail. She has lost confidence in allergists.

Medicines—Usually, she takes (1) a red liquid, 1 tsp. after meals and at bedtime (perhaps elixir of phenobarbital), (2) "some kind of a tal" before meals and at bedtime (likely, DONNATAL® or some "tal" drug), (3) a chalky something 40 minutes after meals and at bedtime (perhaps an aluminum hydroxide preparation), (4) "female shots" for her "change of life condition," and (5) of late, some kind of "town" or "zine." She has five or six kinds of vitamins and "old blood pills" from various doctors, which she never takes. They make her belch.

Food—She often eats little or no breakfast. She avoids meats for fear of hurting her blood pressure. She has to live on sweets.

Operations—At 20, the patient has only her tonsils, teeth and appendix out. At 50, she has had, in addition, her gallbladder removed, a female operation, part of an ovary removed and at least one operation for adhesions. The operation of which she is proudest is the female operation. It was a four-in-one. She does not know what was done.

Family history—The family history, for once, is not noncontributory. Mamma has been nervous all her life. Papa almost had a nervous breakdown. Three brothers have bad stomachs. Two sisters are just like the patient. (Hold it—mamma and the two sisters are waiting to see you when this patient is gone.)

This is no laughing matter. If I did not have these patients I could not make a living.

I took a practice eight years ago in an area given medical care by 10 doctors. No new doctor had been there in 15 years. I was immediately flooded by these patients. Some came like Ponce de León, hoping to find in the new doctor the Fountain of Youth. While I think my fellow physicians are the finest men in the world, I strongly suspect most of the patients were referred to me. Since I was neither prepared nor permitted to operate on them, I had to learn to cope with them.

Out of this experience I have derived some conclusions and pointers which I wish to pass on to you—if by chance you see any of these patients in your practice.

My first conclusion is that these patients are sick—unfortunately, most often incurably sick. They are constitutionally inadequate. They can no more be given a new set of grandparents and parents and a new childhood environment than the far-advanced cancer patient can be given a different type of tissue or the malignant hypertensive a different kidney, sympathetic nervous system and blood vessels. The constitutionally inadequate incurable deserves the same sympathetic study and palliative treatment as any other incurable.

The first principle in treating this patient is: Do no harm. If this patient does not become the victim of multiple surgery, hypnotics, narcotics or alcohol, she will be bothersome but will live more successfully than any other incurable.

The patient is inadequate to stand alone. She must depend. If she does not have a doctor dependency, she will have a drug or quack dependency. The American doctor should prove a safer crutch than the chiropractor, osteopath, faith healer or hypnotic drugs.

If the medical doctor is to hold this patient, he must offer her a positive, continuous program. She must be given a definite time to return to the office each day, each week or each month. This will avoid most night calls and many visits when you are least prepared to see her. You will serve best your needs and hers if you will give her a definite time to return. You may find that a patient who has to come daily will so be able to walk on her own for a month.

On return visits, she should be given positive but not harmful treatment. As the actual history shows, this patient has a poor diet, poor eating habits and poor digestion. Hence, multiple vitamin injections which may not be harmful have more rationale than estrogenic substance which may be harmful. Since nothing is going to help the headache anyway, ASA tablets are much safer to do no good than is DEMEROL®. Elixirs with the B vitamins which are not depressants will most often work as well as elixir of phenobarbital which may further depress an already depressed and unhappy patient. That the treatment is palliative is even more reason it should be safe.

Diets may be put to excellent use in a positive and safe treatment program. Since this incurable is going to spend most of her time treating herself anyway, her struggling with a diet should well give her safe and possibly helpful occupation. She is always either fat, poor or vain. She will welcome a diet suitable to her state. Most drug companies will provide a raft of these charts free of charge.

Further exercise and exercises may prove helpful and rarely are harmful. These patients must have their "low blood pressure" treated. A brisk walk on arising in the morning (rain or shine—insist on it) cannot hurt her blood pressure and may lift her mood.

Who knows? Her pelvic pain may come from poor mood with subsequent poor muscle tone. At least set exercises can do no harm.

If the womb has fallen against the backbone, why not use knee-chest exercises? They may do no good. Neither does suspending the womb, since most often the scar hurts or adhesions give trouble.

A hot bath followed by two aspirin tablets may prove quite as relaxing as THORAZINE®, TOLSEROL® or MILTOWN® and in most areas certainly will be less expensive.

What if the patient will not carry out the outlined physical therapy? She likely will not.

Here a third principle in treating the constitutionally inadequate comes to play: Put the burden of the patient's health on her. These patients are notorious for doctor-shopping. They are disappointed with the doctor because the doctor did not cure them. When the burden of the patient's getting well is put on the patient, the doctor is exonerated if the patient does not get well.

The conversation may go like this:

"How are you today?"

"I ain't a bit better. You just got to do something."

"Have you taken your exercises? Have you walked every morning, rain or shine? Have you stuck with your diet?"

"Well, er—"

Do not let her finish.

"Now, Mary, do exactly what I tell you for four weeks and come back a month from today. You will do it, won't you? I am interested in your doing well."

Let her go.

A fourth principle in treating this patient is: Do not waste your and the patient's time. While I agree with the principle of vocal catharsis, this patient already has made vocal catharsis a vocal cathartic for every doctor in the area. She has reviewed her woes until they have become so fixed that even the psychiatrists send her back to you. In your slack time, get an adequately complete history. If you have no slack time, let an internist get the

data for you. Thereafter, five minutes of sympathetic listening will do more good than 40 minutes of scribbling on a pad and fumbling with correspondence while the patient prattles.

The conversation may go like this:

"Mary, what's giving you the most trouble today?"

"It's my back and that pain in my chest and the smothering."

"Wait a minute, Mary. Let's stick with your back today."

Review her treatment. Point out why she has not improved. Let her get her vitamin shot and go. If you are sympathetic, she will return.

Similarly, do not waste your and the patient's time in useless physical examination. Once a year, do, or let an internist do, a thorough examination. Thereafter, refuse to take the blood pressure or to listen to the heart through a brassière or the lungs through a blouse. When you have told her that her heart is perfect and then listen for defect, you compromise your conviction and hers.

My last suggestion is to give the patient a positive but safe diagnosis. Never argue with this patient. You compromise your dignity and lower her respect for you. She will give her diagnosis. Do not argue, but give your diagnosis more emphatically. Your diagnosis, if safe, will not be an official diagnosis.

The conversation may go like this:

"Well, doctor, what do you find wrong?"

Positively, you reply, "Four things: (1) You do not get enough proper exercise; (2) you do not eat properly; (3) you weigh too much; (4) you are not grateful enough to God.

To say, "You have a little nervousness of the heart" is for her to say, "Oh, I knew I had something wrong with my heart." A diagnosis of "a little liver dysfunction" is to give her another area of symptom fixation. This is safer than some diagnoses because the liver is not likely to get cut out. But to tell her that her womb is prolapsed is to lead her to more surgery.

My final conclusion is that you may learn to appreciate this patient. She will but rarely die, she will never get well, and she will often pay. When you look back over the year, you may discover that you have done quite as much for this patient as for any other.

41st Annual

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Cleveland, Ohio, October 22-25, 1956

The Painful Shoulder

A clinical presentation with a discussion on the various entities afflicting the shoulder joint region—in particular, the soft-tissue lesions and fractures of the upper end of the humerus.

ANTHONY F. DEPALMA, M.D.

James Edwards Professor of Orthopedic Surgery and Head of the Department, Jefferson Medical College, Philadelphia

Scientific Exhibit

Hematuria

M. K. O'HEERON.
JAMES R. FISH AND
JAMES S. BOREN

Houston, Texas

OTHER authors have reported large series of cases of hematuria and emphasized the frequency of various etiologic factors. In this study, emphasis is on the frequency of occurrence of hematuria in each portion of the urinary tract as well as the frequency of occurrence by sex and age.

Definition

Hematuria is defined as any number of red blood cells in an uncentrifuged specimen of urine obtained by (1) voiding in the male or (2) atraumatic catheterization in the female.

Clinical Implications

We have divided hematuria into three classes on the basis of blood loss. This offers a brief guide to initial management of the patient with hematuria. As shown

by the doll figures, the amount of blood lost may vary from no appreciable loss to severe hemorrhage where the immediate concern must be the arrest of a fatal hemorrhage.

GRADE ONE

Grade 1—Amount of blood loss is insignificant.
May be microscopic.
Concern is for etiology.

GRADE TWO

Grade 2—Shock is not imminent.
Transfusions may be required.

GRADE THREE

Grade 3—Blood loss is severe.
Shock is present.
Immediate diagnosis, transfusions and surgery required.

Significance

In children, nephritis was found to be the most frequent cause of hematuria. Infection led the list in all ages and in both sexes in adults. Calculi were the second most common causative agent at all ages in females. In men over 50 years of age, tumors were more common. As expected, trauma was relatively common in young men, and tumors were rare.

Analysis

This study was based on an analysis of 4000 consecutive patients from our private practice. These patients probably represent a cross section of the average urologist's practice, including most of the problems encountered in his day-by-day activity.

Hematuria occurred in 15.07 per cent of the total group of 4000 patients. In more than half of the total group the origin of the hematuria was in the middle urinary tract. Various types of infections accounted for the hematuria in 62.16 per cent of the total group with hematuria. We have broken this down further to show that in the middle urinary tract, infection was the cause in 79.79 per cent, and in the lower urinary tract it was responsible in 65.71 per cent of the patients with hematuria. In the upper urinary tract, calculous disease was the commonest cause of hematuria, accounting for 42.81 per cent of all cases. It is to be noted that the majority of cases of renal calculi also have an associated infection, and in many cases one cannot determine with certainty whether the hematuria was caused by the calculus or by the associated infection.

We have listed all cases of hematuria with calculous disease under the heading of calculous disease regardless of the type or extent of the associated infection. The incidence of calculous disease in the total group of patients with hematuria was 16.85 per cent. In the total group, the other causes of hematuria were: neoplasm 7.04 per cent, trauma 3.85 per cent, systemic causes 0.67 per cent, and miscellaneous (allergy, "March hematuria," etc.) 7.43 per cent.

The largest number of cases of hematuria occurred in the 20 to 39 year age group. In this age group the most frequent cause of hematuria was infection and the next most frequent causes were calculi, trauma and tumor, in that order.

Classification

We have classified hematuria by four methods: (1) origin, (2) type, (3) degree and (4) etiology.

Origin—Figure 1 shows the division of the urinary tract into three portions and the structures comprising each.

Type—Figure 2 illustrates total, initial and terminal hematuria and shows from which structures each may arise.

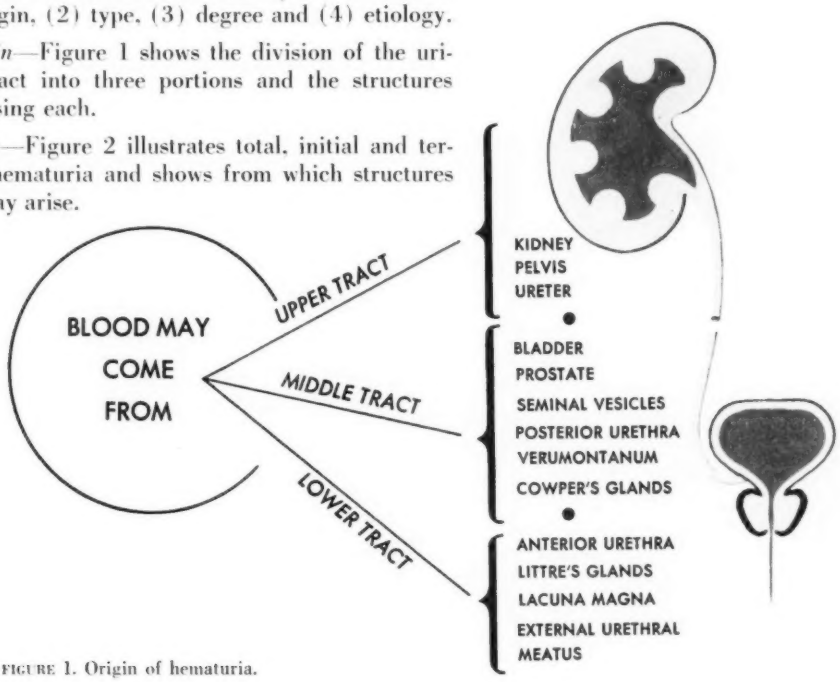


FIGURE 1. Origin of hematuria.

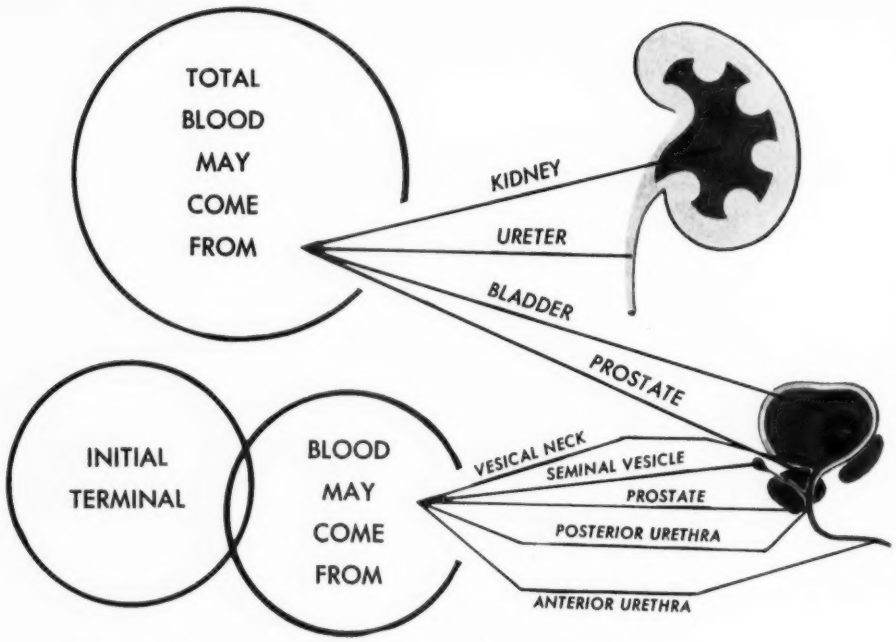
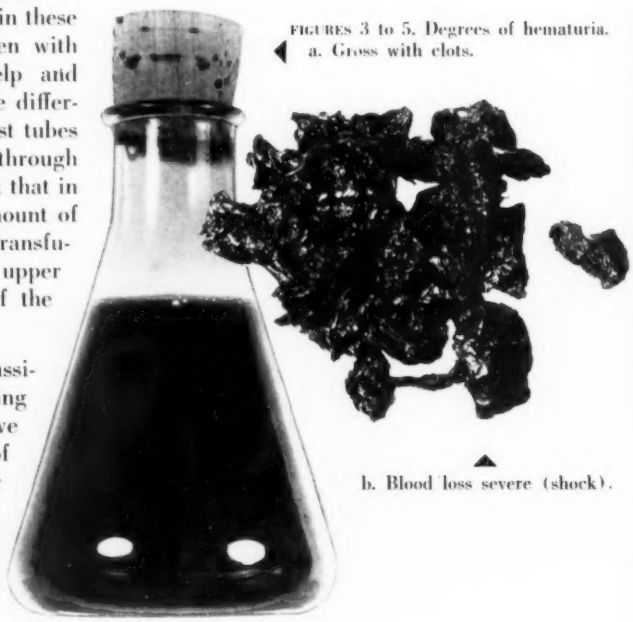


FIGURE 2. Types of hematuria.

Degree—The degrees of hematuria, illustrated in figures 3, 4 and 5, are self-explanatory. It was a difficult problem to dilute blood enough to obtain these microscopic pictures, and even with professional photographic help and color film there was very little difference in the densities in the test tubes of urine shown in figure 5 (A through D), emphasizing the statement that in microscopic hematuria the amount of blood loss is insignificant. Transfusions might be required in the upper three degrees of hematuria if the bleeding is prolonged.

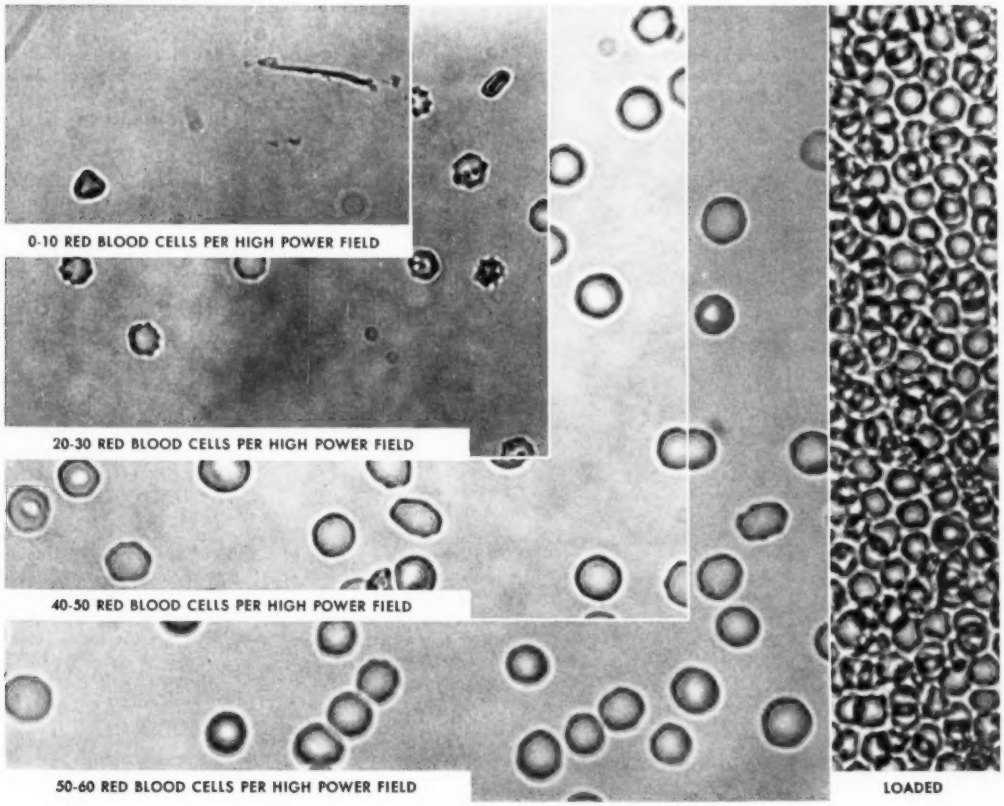
Etiology—The following classification of hematuria according to etiology is a comprehensive listing under each portion of the urinary tract utilizing our headings of infection, neoplasms, calculi, trauma, systemic and miscellaneous.



FIGURES 3 to 5. Degrees of hematuria.
a. Gross with clots.
b. Blood loss severe (shock).

FIGURE 4. Gross without clots. Blood loss moderate (shock if prolonged).

FIGURE 5. Microscopic. Blood loss insignificant.


0-10 RED BLOOD CELLS PER HIGH POWER FIELD
20-30 RED BLOOD CELLS PER HIGH POWER FIELD
40-50 RED BLOOD CELLS PER HIGH POWER FIELD
50-60 RED BLOOD CELLS PER HIGH POWER FIELD
LOADED

Causes of Hematuria

	Upper Urinary Tract	*Middle Urinary Tract*	*Lower Urinary Tract*
INFECTION	Acute pyelonephritis Acute and chronic nephritis Pyonephrosis Pyelitis cystica Ureteritis cystica Appendicitis Papillitis • Tuberculosis Renal abscess Salpingitis Pelvic abscess	Cystitis Prostatitis Urethritis Seminal vesiculitis Tuberculosis Intestinal diverticulitis Bilharziasis	Urethritis Periurethritis Periurethral abscess Verruca Chancre Chancroid Granuloma Tuberculosis
NEOPLASMS	Wilms' tumor Hypernephroma Angioma Papilloma Benign adenoma Papillary carcinoma Squamous carcinoma Metastatic carcinoma Sarcoma	Polyps • Papilloma Carcinoma Metastatic carcinoma Sarcoma	Polyps Papilloma Carcinoma Nevus Metastatic carcinoma
TRAUMA	Internal trauma (surgery, instrumentation) Contusion Perforating wound Intra- or extracapsular rupture	Instrumentation Wounds Perversion	Internal trauma (instrumentation, wounds, perversion) External trauma (contusion, laceration, fracture)
CALCULUS	Pelvic Branched Stag-horn Cortical	Prostatic Urethral Bladder	
SYSTEMIC	Arteriosclerosis Allergy Circulatory (backward failure with chronic passive congestion) Typhoid Smallpox Malaria Yellow fever Lupus erythematosus Periarteritis nodosa Lues Aneurysm of renal artery Pharmacologic (sulfonamide drugs, cantharides, anticoagulants, quinine, mushroom poisoning, phenol, turpentine, spider bites)	Arteriosclerosis Allergy Lupus erythematosus Periarteritis nodosa Lues Pharmacologic (sulfonamide drugs, cantharides, anticoagulants, turpentine) Blood dyscrasias (sickle cell anemia, leukemia, erythroblastosis fetalis, thrombocytopenic purpura, scurvy, polycythemia vera, vitamin K deficiency)	Arteriosclerosis Allergy Lupus erythematosus Periarteritis nodosa Lues Pharmacologic (sulfonamide drugs, cantharides, anticoagulants, turpentine) Blood dyscrasias (sickle cell anemia, leukemia, erythroblastosis fetalis, thrombocytopenic purpura, scurvy, polycythemia vera, vitamin K deficiency)

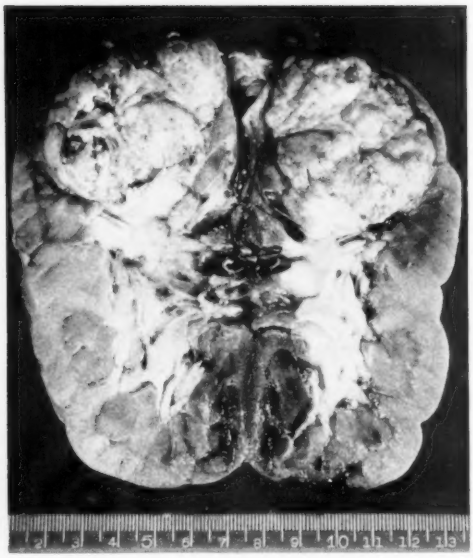
CAUSES OF HEMATURIA *(Continued)*

	Upper Urinary Tract	*Middle Urinary Tract*	*Lower Urinary Tract*
SYSTEMIC *(Continued)*	Blood dyscrasias (sickle cell anemia, leukemia, erythroblastosis fetalis, thrombocytopenic purpura, scurvy, polycythemia vera, vitamin K deficiency)		
MISCELLANEOUS	Postoperative Hydronephrosis Cystic diseases Anomalies Oxaluria Varicosities Stricture Essential hematuria Renal infarction Thrombosis of renal vein Physical exertion (March hematuria) Dehydration Foreign bodies Diverticulum Endometriosis	Postoperative Varicosities Foreign bodies Stricture Leukoplakia Fistula Diverticulum Endometriosis	Stricture Postoperative Foreign bodies Caruncle Fistula Leukoplakia Diverticulum

The following photographs and drawings illustrate representative pathology from our practice. In all the illustrated cases, hematuria of varying degree was an initial objective finding.

UPPER URINARY TRACT

Solitary renal cyst



Renal carcinoma

Hydronephrosis

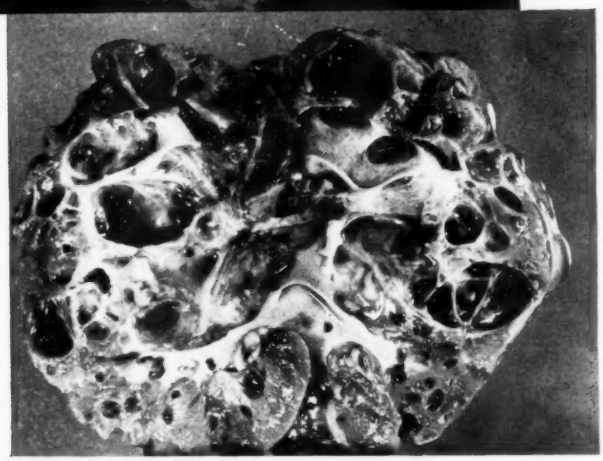
Hypernephroma

Stag-horn calculus

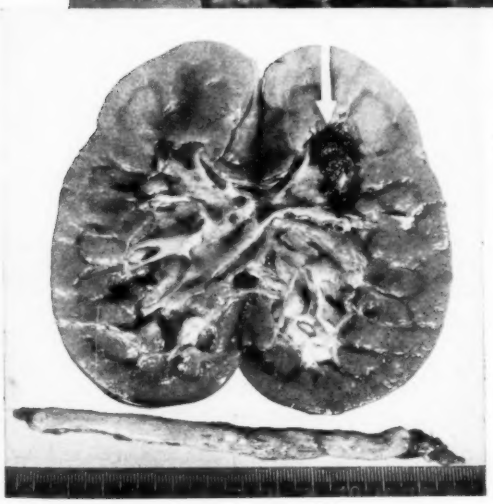
UPPER URINARY TRACT

UPPER URINARY TRACT

Renal calculi



Polycystic disease



Hemangioma

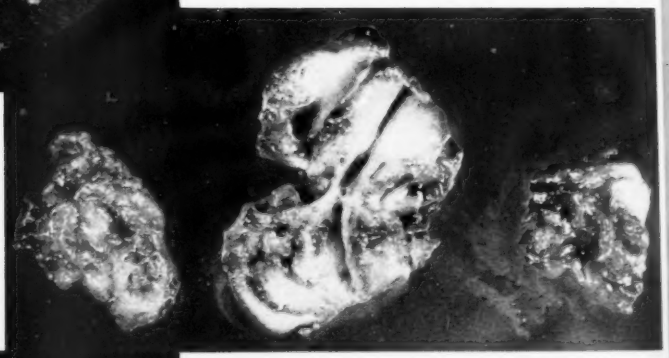
Ureteral polyps

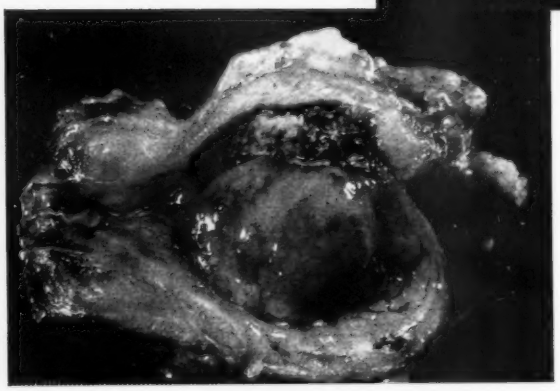
MIDDLE URINARY TRACT

Benign prostatic hypertrophy ▶

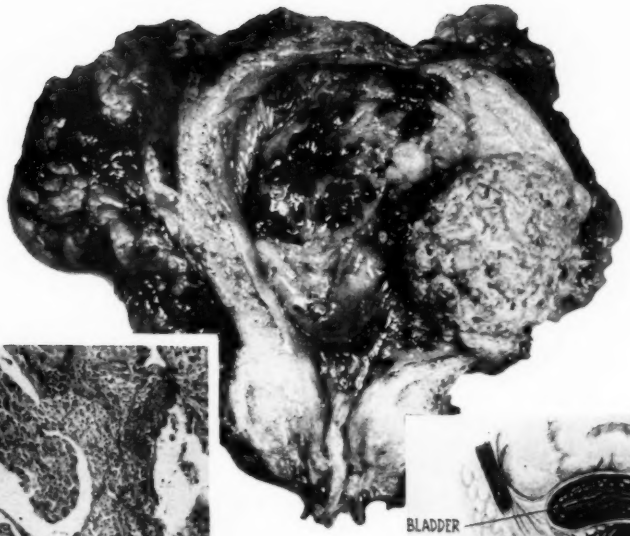
◀ Urinary bladder calculus

Prostatic calculi ▶

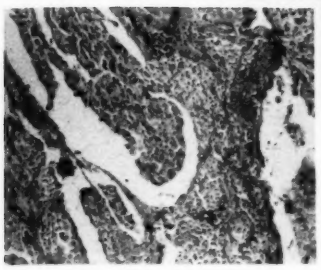


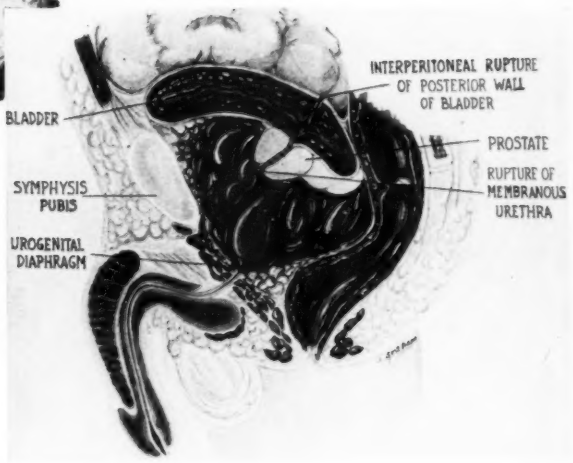


◀ Urinary bladder carcinoma



◀ Urinary bladder carcinoma





Urinary bladder rupture ▶

LOWER URINARY TRACT

Fracture of penis

Urethral caruncle

Carcinoma of penis

Diagnostic Procedures

Preliminary history and physical examination are accomplished, with emphasis on the urologic symptoms and anatomy. Routine laboratory tests are performed as soon as possible and special tests ordered when indicated. As mentioned previously, bleeding may be so severe as to constitute an emergency and much preliminary work may have to be eliminated.

The flat plate of the abdomen, the KUB or the preliminary x-ray usually precedes pyelography. The one illustrated here (preliminary x-ray) shows bone metastasis of prostatic carcinoma. Conditions permitting, an excretory urogram may be performed; the urogram shown reveals a left hydro-ureter and hydronephrosis following obstruction at the ureterovesical junction.

Additional procedures are then performed as indicated.

PRELIMINARY

Preliminary x-ray

Excretory urogram

ADDITIONAL PROCEDURES

Cystogram revealing marked trabeculation and cellule formation.

Urethrograms are sometimes made. This one represents extravasation due to rupture of the urethra at the apex of the prostate, frequently associated with pelvic fractures.

Vesiculogram in this case shows empyema of the seminal vesicles.

An aortogram is sometimes indicated, and here is shown puddling of dye in a large left renal carcinoma.

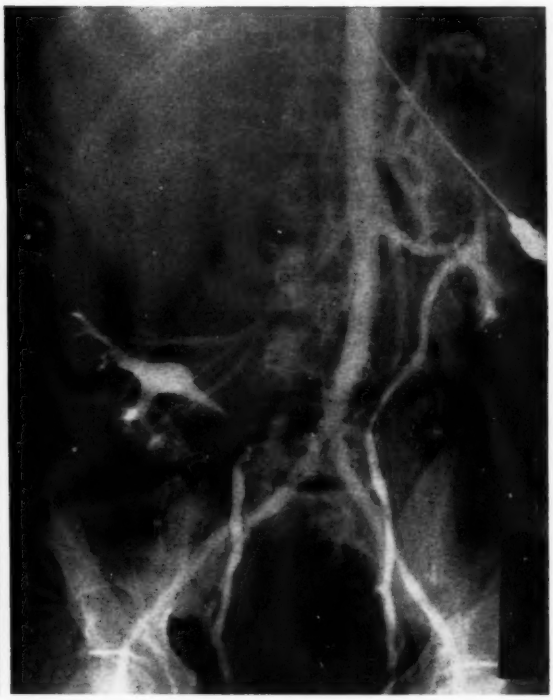
A presacral pneumoretroperitoneogram facilitates visualization of an enlarged kidney, this one on the right. This case proved to be a carcinoma of the upper pole of the kidney.

Presacral pneumoretroperitoneogram plus aortogram. This enlarged left kidney was not explored, as it proved to be an attempt at duplication.

Air pyelogram, which is sometimes helpful in diagnosis of tumors and nonopaque calculi.

Retrograde pyelography is generally our most satisfactory method of investigating the upper urinary tract. This patient had a large right hydronephrosis which was repaired by reimplantation of the ureter with excision of the redundant pelvis.

Excretory urogram following presacral air injection was employed to show enlargement of the upper pole due to carcinoma.



The effects of a large carcinoma (probably adrenal) are demonstrated by combining retrograde pyelography, aortography and presacral air injection. With proper technic, most of the air usually can be made to outline the side desired. In this case, adhesions and extension of the tumor prevented the air from ascending on the right.

Conclusions

1. Hematuria usually indicates disease of the urinary tract.
2. Every case of hematuria must be explained.
3. Control of hemorrhage and blood replacement may take precedence over diagnosis.
4. Hematuria occurred in 15.07 per cent of 4000 urology patients.
5. In our study the most common causes of hematuria were infection, calculous disease and neoplasm.

SYMPOSIUM

Ulcers and Cancer of the Stomach

WARREN H. COLE,[1] WALTER L. PALMER[2] AND WARREN W. FUREY[3]

WARREN H. COLE

WALTER L. PALMER

WARREN W. FUREY

Introduction (Warren H. Cole, Moderator)

WE are going to limit most of our discussion to ulcer of the stomach, mentioning duodenal ulcer only briefly. Cancer of the stomach will be considered, since it is so common and so important. When all the panel members have completed their presentations, we will answer your questions.

Roentgenologic Factors (Warren W. Furey)

The study of gastrointestinal conditions in general and stomach disorders in particular constitutes a large part of the radiologist's everyday work. Gastric ulcer and gastric cancer have been matters of serious concern for many years, and in spite of great medical progress they remain major diagnostic and therapeutic problems.

The x-ray diagnostic criteria have not changed appreciably through the years, although certain technical improvements, including the spot-film device and the image-amplifying fluoroscope, have been helpful.

Usually, demonstration of the ulcer crater is the radiologist's primary concern, and in many instances this is very simple. Sometimes, however, it may be not only difficult but impossi-

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Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

ble. The patient may have been under medical management and the ulcer may have healed rapidly, with resultant disappearance of the crater.

Having found a crater, however, distinguishing between malignancy and benignancy is of serious concern. Various statistics indicate that approximately 5 per cent of ulcers of the stomach are malignant. Craters situated away from the lesser curvature, particularly in the prepyloric area, should be considered potentially malignant. Those remote from the curvature and having irregular, erosed edges with evidence of induration, some exhibiting a meniscus sign, deserve very serious further consideration. We recommend utilizing various processes if there is any doubt—all clinical evidence possible, gastroscopy, a test of medical management and, last but not least, surgical exploration. In my opinion such surgical intervention is not only justified but it is to be preferred to any unnecessary or unwarranted delay. Such delay may result in the development of a malignancy, and may mean the difference between life and death for the patient.

Additional new problems have come our way. I refer to the introduction of cortisone, ACTH and other similar preparations. Use of these agents has resulted, in some instances, in development of ulcers which previously were not present or not suspected, and as a rule most such ulcers are silent until something catastrophic happens.

Another addition to the problem, as far as I personally am concerned, is the increasing incidence of gastric ulcer in patients who have been subjected to resection. I will say something about that later.

Malignancy other than malignant ulcer is not, as a rule, too much of a radiologic problem, particularly in the more advanced stages. However, the very early stages of malignancy may give the false security of a negative x-ray examination, and I warn you to beware of such negatives. If clinical evidence persists, even in the face of a negative x-ray examination—if the patient is having continued distress, with beginning deterioration, loss of weight, continued loss of appetite—another x-ray examination is a must, because such findings may be the result of a developing malignancy.

A patient whom we had treated for duodenal ulcer over a long period—and by that I mean years—had a recurrence, and we suspected that duodenal ulcer was again present. The patient did not respond immediately, and x-ray examination disclosed a defect high on the lesser curvature of the stomach, contrary to what we had been finding in the past. The defect had a rather smooth, rounded edge and

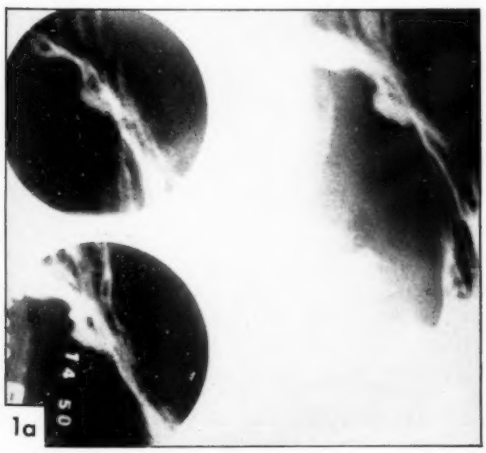

FIGURE 1a. Ulcer crater on lesser curvature.

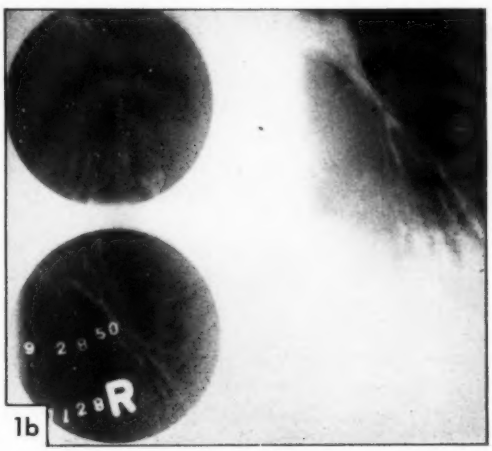

FIGURE 1b. Disappearance after two weeks' management.

was somewhat irregular and erosed on the outer edge (figure 1). However, after only two weeks' medical management, the crater disappeared almost completely. This favorable response usually is considered to rule out a malignancy, although it is not an absolute criterion. It is one that we do use, however, and recommend whenever we see evidence of a gastric ulcer. This patient improved very well on medical management, and as far as we know has not had a recurrence since 1950.

A slightly different case concerned another patient whom we had observed for many years, a woman about 42 years old. The large ulcer crater shown in figure 2, situated in the midportion of the lesser curvature of the stomach, was somewhat irregular. This irregularity, however, proved to be due to the presence of foreign material within the crater. One might ask whether the size of this ulcer has any significance in regard to malignancy. In this particular case, with its known duration of several years and with no particular improvement on medical management, it would not be significant unless you believe that many of these ulcers might become malignant. Personally, I do not subscribe to that idea.

The film shown in figure 3 was made one year later. The crater still was about the same size, and medical management was not appreciably effective. I might add that in these cases the lack of improvement on a medical regimen can be deceiving. This patient never actually followed the regimen prescribed, and when she was hospitalized and given properly supervised medical management the crater did decrease in size, although it did not disappear.

The patient refused surgery for several years. Finally, in 1950, four years after the film in figure 3 was made, resection was performed. Despite its long duration, it was still a benign ulcer.

The patient whose films are shown in figures 4 and 5 first came to us in 1943. The film in figure 4 was made in 1945. She had been told she had a malignancy of the pyloric end of the stomach. You might ask why. Well, the pyloric end of the stomach was definitely nar-

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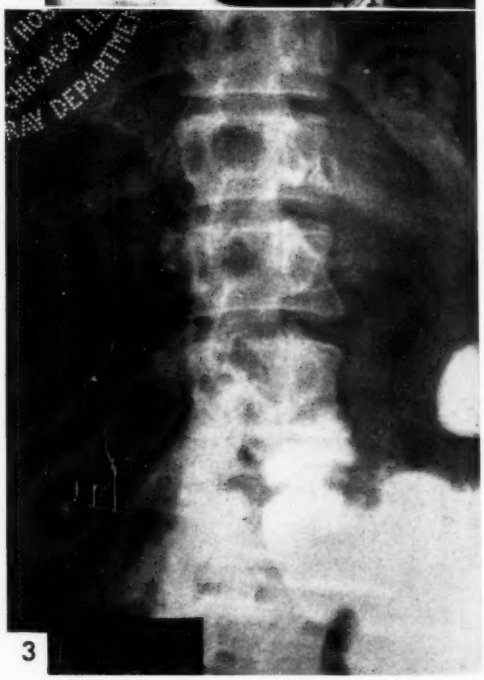

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FIGURES 2 and 3. Large ulcer crater, no improvement on medical management. Benign ulcer found after resection.

rowed—not particularly irregular, however. In view of her history of having had this defect for more than two years without change, we concluded it could not possibly be a malignancy. We could not come up with a definite diagnosis. We suspected there might be a congenital band, or an ulcer with scar tissue—we could not say what it was, but we were convinced it was benign.

The film in figure 5 was made in 1947, two years later. Her symptoms had recurred and she came in immediately. We demonstrated a very small crater of a benign ulcer. Ulcers on the lesser curvature very commonly are associated with spasm of the pylorus and prepyloric area. Certainly an ulcer in this area might well be accompanied by scar-tissue formation. At any rate we think we can satisfactorily conclude that this was a benign recurring gastric ulcer.

The next case represents one of the new problems I mentioned. The patient, a 42 year old man, had had a serious hip fracture as a youngster, and a rather severe arthritis deformans of the hip had resulted, with deformity of the spine. He had all the manifestations of long-standing arthritis. He was ultimately given cortisone, and in January 1955 had a gastric hemorrhage. Examination shortly thereafter revealed a small projection from the lesser curvature of the stomach which was interpreted as a benign gastric ulcer. There was no evidence of surrounding induration. Medical management was instituted, cortisone was discontinued, and a film made in July 1955 showed complete disappearance of the crater.

Figure 6 illustrates a very large crater slightly off the lesser curvature of the stomach toward the posterior wall. The patient was a white woman in her early fifties with long-standing rheumatoid arthritis who had been on cortisone for about two years. She, too, had a rather severe gastric hemorrhage and came to the hospital after about three weeks of medical management. The size of the crater and its location, off the lesser curvature, might suggest the possibility of malignancy; however, we did not see any particular change in mucosal pattern.

A spot film made at fluoroscopy still showed the large crater; with the patient turned a lit-

FIGURES 4 and 5. Pyloric constriction of undetermined origin. Second film about two years later shows an ulcer crater on lesser curvature.

tle further, it fitted more to the lesser curvature. The history of cortisone therapy led to the conclusion that this was a cortisone-type ulcer. Unfortunately, since discontinuance of cortisone the patient is again crippled and she has been unable to return to the hospital for further examination. A film made about two years before this incident did not show any evidence of ulcer.

The next illustration is a favorite of mine. I do not advocate this type of diagnosis. The patient was admitted to the hospital on a Saturday morning for a routine gastrointestinal examination. Films showed an ulcer crater near the lesser curvature of the pylorus. We sent her home, and she came back on Monday morning to have a barium enema, but at 48 hour fluoroscopy there was almost complete retention. The residual barium in the stomach perforated out into the abdomen, surrounding the cecum and the adnexa (figure 7). This is one of those tragic things we do see, and I present it as a caution.

The crater in the next case is not unlike the one shown in figure 1. However, the patient, whom we had had under management over varying periods for recurring ulcer, came in with some change in symptoms. Pain was more severe, she had a distaste for food and she had lost weight. We found a large, irregular crater, surrounded by definite evidence of induration and thickening of the mucosa (figure 8), suggesting a malignancy.

The patient refused gastroscopy, refused anything but medical management, and came back in two months. The crater had disappeared, but in its place was a definite filling defect high on the lesser curvature, along with mucosal changes (figure 9), further confirming that the patient did have a malignant ulcer originally, and this was the resultant malignancy. She eventually submitted to resection, and the malignancy was proved microscopically.

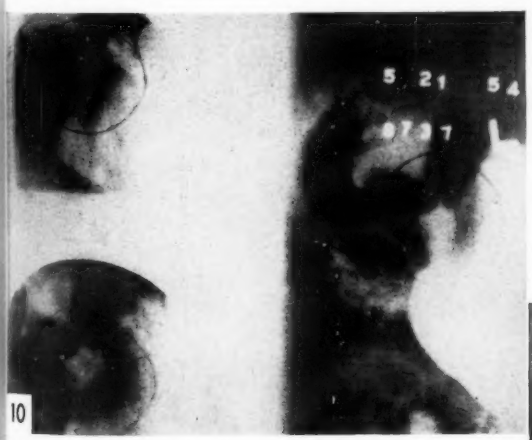
Another interesting case is that of a patient who also had been under observation for many years and who had learned, through the years of recurring duodenal incidents, to go on his diet every time he had recurring pain. He

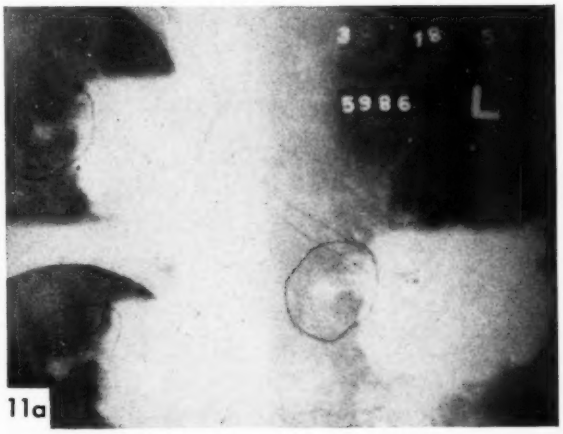
FIGURE 7. Gastric ulcer with perforation showing free barium in the abdominal cavity.

FIGURE 6 *(left)*. Large crater in upper stomach of patient who had been treated with cortisone.

FIGURES 8 and 9. Malignant ulcer crater on lesser curvature. Two months of medical management were followed by an excavation at the ulcer site.

FIGURES 10 and 11a and b. Prepyloric malignant ulcer, posterior wall. Benign ulcer on lesser curvature of resected stomach 10 months later.





managed fairly well until one such incident when his regular regimen did not bring relief. We studied him fluoroscopically and noted a defect in the stomach not seen previously in his case. In the prepyloric area on the posterior wall was an ulcer (figure 10). The outline was irregular and the mucosa did not conform to the stellate shape we usually expect in a benign ulcer crater, and because of that we suggested a diagnosis of a malignant ulcer. Resection was done, and a year later we were surprised to find, on examination when pain recurred, another ulcer crater, one of those recurrences in a resected stomach (figure 11).

We have encountered two types of patients who frequently have trouble following resection. One is the patient who has a natural ulcer-forming predisposition, particularly of the duodenum. The other type has an utter disregard for things he cannot do following resection; he goes ahead and does them and the result is an ulcer.

An 84 year old white man came in with a definite defect on the greater curvature of the stomach. As far as we could tell, without pressure or spot filming, it was perfectly smooth. One might well suspect it was benign (figure 12). However, on pressure with spot filming we did find definite induration, with changes in mucosal pattern. Further, unlike usual craters on the lesser curvature projecting outward, this one projected inward—and that again speaks for potential malignancy. Local resection was done in January 1953. The patient had an uneventful recovery.

The next case emphasizes one of the cautions I would warn you about. The patient complained bitterly of stomach trouble in June 1952. He is a friend of too many doctors. He was sent in for an examination, which was done outside the hospital. An apparently normal stomach was found—at least that is what he was told at that time. The following year, on April 30, 1953, he came in and we found a tremendous filling defect involving both the greater and lesser curvatures, and I think anyone who had seen many of these would agree with the diagnosis of a malignancy. A spot film showed irregularity along both curvatures. In the face of a suspicious

FIGURE 12. Large malignant ulcer, greater curvature.

clinical history and other findings, a negative examination should be disregarded and the examination repeated sooner than was done in this case. In spite of the fact that examination was repeated within 10 months, a lesion had developed which was unresectable; it was fixed and had metastasized to the surrounding lymph glands.

Malignancy is not confined to the aged. A 21 year old nurse who had undergone operation about six months previously because of gallbladder complaint came in with continued symptoms, and at x-ray examination a large defect was found which proved to be a scirrhous carcinoma.

The large ulcer crater shown in figure 13, irregularly outlined, again shows marked induration, the so-called kissing type or saddle ulcer. It was resected as an ulcer. It proved to be a large malignant ulcer but not a carcinoma—it was a reticulum cell sarcoma.

DR. COLE: Dr. Furey specifically brought out the point that there are gastric ulcers which have the appearance of a crater, but without hyperplasia, and which may be benign or malignant. Keep that in mind as the discussion continues—that actually there are two types of carcinoma from the anatomic or

FIGURE 13. Large ulcerating reticulum cell sarcoma.

gross standpoint. One is a proliferative lesion; the other is a crater-type lesion which looks like a benign ulcer but may have malignancy in its base.

Medical Aspects
(Walter L. Palmer)

I would like first to comment on Dr. Cole's remark concerning the difference in types of gastric cancer. Using Broders' index, grade 1 and 2 tumors (a low percentage of undifferentiation) carry a five year survival rate after resection of about 60 per cent and a 10 year rate of 50 per cent. Grade 4 tumors, with a high degree of undifferentiated cells, have a five year survival rate of only 21 per cent and a 10 year rate of 15 per cent. Similar differences are apparent if one uses the gross classification of Bormann. The polypoid, nonulcerative type is relatively infrequent and yet it has the highest percentage of surgical cure. The second type, an ulcerated but a sharply circumscribed neoplasm, also has a high curability rate. Types 3 and 4 of Bormann, the infiltrating tumors, have a serious prognosis. In one series of type 4 tumors there were no survivals after five years.

Different gastric cancers vary greatly in rate of growth. Some may be truly called chronic cancers, and others develop rapidly and are acutely malignant.

An illustration of slow-growing "chronic" cancer is the case of a patient who was first seen in September 1931 by Dr. George Eustermann. The history was of indigestion of seven years' duration. A mass was palpable in the epigastrium, and extensive deformity was seen by x-ray. The patient refused operation, and in the ensuing two years gained 16 lb. In April 1934, two and a half years later, symptoms recurred with a massive hemorrhage, and the patient accepted the recommendation of operation. Subtotal gastrectomy was performed, and an ulcerated polypoid adenocarcinoma measuring 10 by 7 by 3 cm. found. In 1943 the patient was still in good health at age 75. I corresponded with him two and a half years later, in 1945, and he was still alive and in good health. So here is a patient whose tumor was resected nine and a half years after the onset of symptoms and yet he was in good health 11 years after operation, 19 years after onset of symptoms.

One of our patients had an ulcerating carcinoma correctly diagnosed by x-ray in 1938. The ulcer niche did not disappear completely. In other words, the deformity of the stomach persisted in the way Dr. Furey has described, confirming the roentgenologic diagnosis of carcinoma. The gastroscopist also diagnosed carcinoma, but the patient had no symptoms, felt well and refused operation. Time went by, with some variation in the size of the niche at examination in October 1938, October 1939, January 1940, June 1941 and August 1942, but the lesion never disappeared. Finally the patient consented to operation. A rather small ulcer was found, with infiltration about the edge. Histologic study disclosed an ulcerating colloid carcinoma of the stomach. The lesion was removed in 1942 after a known existence of four years, and yet the patient is perfectly well today, without signs of recurrence. These, then, are two unusual cases of chronic, slow-growing gastric cancer.

The other extreme is illustrated by a patient seen in November 1938 with a small, rather benign-appearing niche of the lesser curvature of the stomach as seen by x-ray.

Symptoms had been present for only 18 months. Gastroscopically the lesion was interpreted as malignant. Skeletal metastases were demonstrated radiologically. At autopsy, the lesion in the stomach looked very much like a benign ulcer. All the muscular layers of the gastric wall had been interrupted. Neoplastic cells were present along the edge and in the lymphatics. This was a rapidly growing tumor. In 18 months, as nearly as could be judged, the symptoms appeared and the lesion spread rapidly through the body and caused death. This is the so-called rapidly metastasizing type of gastric cancer described by Jarcho. I doubt if we can ever cure it with surgery. The other kind, the "chronic" type, can be cured with surgery. The majority of gastric cancers fall between these extremes of relative benignancy and malignancy.

Now I would like to discuss the alleged malignant transformation of benign ulcers. I agree with Dr. Furey that there is no satisfactory proof that benign ulcers undergo malignant change. However, there are clinical situations which suggest that and from which such a conclusion has been drawn. One such patient was found by Smith and Jordan in an analysis of a large series of cases of gastric ulcer. The patient had a gastric ulcer at the age of 52 which healed without recurrence. At age 65 a cholecystectomy was performed and no gastric lesion was found. At the age of 72 the patient had rather profound mental deterioration. Gastric symptoms developed at age 75, 23 years after the gastric ulcer; death resulted from cerebral hemorrhage. At autopsy there was a carcinoma of the stomach, carcinoma simplex with mucinous foci; no ulcer or ulcer scar was found. Hence, the authors suggested that perhaps this carcinoma had developed on the base of the pre-existing benign ulcer, pre-existing by 23 years.

The difficulties in interpreting such a situation are illustrated by a sketch of a portion of a stomach resected in about 1924. Three different lesions were present—a benign ulcer, a small polyp essentially benign under histologic examination, and a small ulcerated polyp with the characteristics of a frank adenocarcinoma including carcinoma cells in the lymphatics and in the serosa of the stomach. The patient died 18 months later from metastases. This case is very instructive because it shows how difficult it is to be sure whether a lesion developing in the stomach really begins in the benign ulcer, or in areas adjacent to it or distant from it and then spreads to involve it.

There is another mechanism operative in the formation of ulcerating carcinomas which look like benign ulcers, and that is peptic digestion of the necrotic tissue in the base of the carcinoma and, indeed, peptic digestion of the wall extending beyond the neoplasm. The peptic ulceration of malignant ulcers may heal, but rarely completely.

I completely agree with Dr. Furey in regard to the importance of demonstrating the complete disappearance of the ulcer crater roentgenologically and, if possible, also gastroscopically.

Another point of some interest concerns the role of acid gastric juice in the chronicity of benign ulcer, in its recurrence and in its pathogenesis. The production of complete achlorhydria for three months or longer has resulted invariably, in our experience, in healing of the ulcer and in persistence of the healing for the duration of the achlorhydria. This fact shows the dependence of chronic gastric ulcer on the presence of acid gastric juice.

The problem with respect to ulcer and carcinoma is not whether ulcers degenerate into carcinoma, but rather how to make a correct differential diagnosis. As Dr. Furey pointed out, this may be extremely difficult. Some surgeons and some internists take the view that because of this difficulty all ulcerating gastric lesions should be resected. We do not take that view, because we think that with careful study and follow-up it is possible to make this differentiation in a high percentage of cases. In 121 patients reported by Dr. Kirsner, Dr. Levin and myself in 1954, patients in whom we had arrived at a diagnosis of benign ulcer as indicated by our employment of radiation therapy as a part of the therapeutic program, we made five errors; in other words, in 4 per cent our diagnosis was incorrect and carcinoma was later found to be present.

It can be argued that resection is very good treatment for benign ulcer and hence is indicated for all gastric ulcers. Rarely, if ever, does an ulcer recur after resection for benign gastric ulcer. Most of the recurrences are after resection for duodenal ulcer. Was the recurrence you mentioned after resection for gastric ulcer, Dr. Furey?

DR. FUREY: After gastric carcinoma.

DR. PALMER: That is even rarer.

Another consideration is that sometimes the dumping syndrome, the so-called postgastrectomy syndrome, is just about as bad as the carcinoma; it certainly is worse than a benign ulcer. If one could be sure that symptoms of that sort would not appear, I think one would be much quicker to recommend resection.

Surgical Considerations (Warren H. Cole)

First I would like to call your attention to the low resectability rate for cancer of the stomach. In the large series which Pack and McNear studied a short time ago, it was only 40 per cent. Their five year survival rate was 34.7 per cent after operation, which is higher than most figures quoted. Dr. Ransom of Michigan reported a resectability rate of only 36 per cent in a large series. That means, of course, that the patients are getting to the operating table too slowly.

The duration of symptoms before the patient consults a physician or before he comes to the operating room is rather important. Gray and Ward recently brought out that point. The average duration of symptoms before their patients consulted a physician was 7.8 months, and it is an astounding fact, too, that after the patients had consulted physicians an average of 6.4 months elapsed before the patients reached the operating room. These were frank carcinomas of the stomach. I think you will agree that this is a very lamentable situation and we ought to do our best to change that figure of 6.4 months' delay.

Dr. Palmer and Dr. Furey both mentioned the difficulty in distinguishing between benign gastric ulcer and malignant gastric ulcer. (I would like to emphasize again that we are talking here about crater ulcers and are not including proliferative cancer.) A couple of very fine articles, one by Welch and Allen of Boston and another by Grimes and Bell on the opposite coast of the United States, emphasize this difficulty. Welch and Allen found an incidence of massive hemorrhage of 9 per cent in benign ulcer and 6 per cent in malignant ulcer, a difference which is not significant. The incidence of perforation in those two types of ulcer was the same. The size of the ulcer, as Dr. Furey already has mentioned, was of no value in differentiation. In Welch and Allen's series the average size was 1.6 cm. for benign ulcers and 1.7 cm. for malignant ulcers. Grimes and Bell, going at it slightly differently, found that 75 per cent of the benign ulcers in their series had a diameter less than 3 cm., whereas 71 per cent of the malignant ulcers were less than 3 cm. in diameter. Likewise, the same percentage of patients in the two groups had absence of free acid, namely, 20 per cent, although Welch and Allen did comment that it appeared from their data that the absence of free acid after histamine was suggestive of malignancy.

Waugh and associates noted that 65 per cent of their patients with malignant gastric ulcer had normal acidity—which, as I said, is confusing from the diagnostic standpoint. In 71 patients whom Waugh and associates studied, the average duration of symptoms in the cases of malignant ulcer was 38 months. This corresponds with some of the cases Dr. Palmer described and, of course, differs from the duration of symptoms in frank hyperplastic carcinoma which I mentioned, namely, an average of 7.8 months.

Another point I was not familiar with, and I wish Dr. Furey would comment on it later, is that in Waugh's series 22 per cent of the patients with malignant gastric ulcer also had a duodenal ulcer. I was not aware of that relationship—meaning that the mere fact a patient has a duodenal ulcer does not prove he does not also have a gastric ulcer.

An important feature which has cropped up in nearly all articles dealing with peptic ulcer is that the errors made by the roentgenologist are really considerable. We will ask Dr. Furey about that, too. I do not recall that he men-

tioned the incidence of diagnostic error in differentiating the two types of ulcer. Most of the articles which comment on that give figures ranging from 10 to 12 per cent error, meaning that in 100 consecutive cases diagnosed benign gastric ulcer by the radiologist, 10 to 12 will turn out to be malignant ulcer.

Especially important is the fact that in Waugh's series the five year survival rate was 50 per cent, much better than that for hyperplastic polypoid carcinomas (approximately 25 per cent). This is another reason we should not misdiagnose malignant gastric ulcers and procrastinate with them. Sixty per cent of these patients with malignant ulcer had typical ulcer symptoms, so that one could not differentiate on that basis.

Another point, which Dr. Palmer may be sorry I brought up, deals with a study at the Mayo Clinic by an internist and a surgeon. They followed 414 patients with gastric ulcer for five years and reported that only 20 per cent had a satisfactory result, and in 33.8 per cent medical treatment was abandoned in favor of surgery; carcinoma was present or developed in 10.4 per cent of that group at the end of five years. In 140 patients who were treated initially by operation, 24.3 per cent had a carcinoma. That does not mean that 24 per cent of gastric ulcers are malignant, because patients in this group were somewhat carefully selected. If I were asked what percentage of gastric ulcers are malignant, I would place the figure somewhere between 10 per cent (which is the error made by the radiologist) and 24 per cent, which was the incidence found in the Mayo Clinic series; perhaps it would be 15 or 16 per cent. I am going to ask the panel members to comment on that later.

Now one or two brief remarks about surgical treatment. As you see, I am building up to a rather radical philosophy in regard to treatment of gastric ulcer, but I would not say that all patients with gastric ulcer should have operation. I would agree that young patients who have a short history of ulcer and perhaps some definite reason for it could be considered as having benign lesions and be put on a trial therapy; yet, in a series reported by Gray and associates, 8 per cent of the malignant ulcers appeared in patients less than 40 years old, so you cannot exclude them completely in young persons. I should think that if you are going to treat any of them medically, young patients with short histories might be candidates; however, I am not very willing to treat these patients very long unless therapy is remarkably effective. It is a terrific responsibility to treat gastric ulcers medically, because if you find out a few months after initiation of treatment that you were mistaken and the ulcer was malignant instead of benign, you may have signed the death warrant by the delay.

If you operate, what type of operation? Most surgeons resort to subtotal gastric resection; if the ulcer is malignant and high, we might do a total gastric resection. I agree with Dr. Palmer that many patients with total gastric resection have postoperative symptoms. I do not like to do total resection and will not do it unless I am positive the lesion is malignant. If an ulcer were high on the lesser curvature, for example, and I did not know what it was, I would excise it and send it to the laboratory for a frozen section. I will admit that frozen sections in gastric ulcer are not 100 per cent accurate by any means, but they are better than our eyes.

One of the cases of gastric carcinoma which Dr. Palmer referred to as probably incurable no matter what type of therapy one utilizes is shown by one of our patients who had had symptoms for only six months. We did a subtotal gastrectomy and found a clean-cut ulcer. I thought when I saw it that it was a plain benign gastric ulcer and that we could cure the patient. Microscopic section revealed numerous highly malignant cells. In six months the patient was dead.

Dr. Eustermann in his publications has referred to gastric ulcers which disappeared under treatment, recurring a few weeks later. In one such case, they finally operated several weeks or a few months later and found that the ulcer was malignant. Good medical treatment can make a malignant ulcer disappear—or maybe it fills up with cancer cells, we do not know which.

FIGURE 14. Ulcer in the midportion of the lesser curvature was average in size. Trial medical therapy brought improvement in symptoms, and healing appeared to take place.

Figure 14, a film made October 20, 1953, illustrates that point. Here is a gastric ulcer, a pretty good deformity. A trial of medical therapy was instituted, and about seven weeks later it appeared that healing had taken place. At 10 weeks no evidence of ulcer could be found (figure 15). We did a resection, however. Our medical people are rather surgical-minded on these, and they asked me to see the patient. Somehow I did not like the idea of treating that patient further medically, even though the ulcer had disappeared, so I recommended operation. Microscopic examination showed typical malignant cells. The patient had a malignant ulcer which had filled up with some fibrin. I can easily see how the x-ray people never could have seen that ulcer. The operation was performed too recently to know what is going to happen to the patient.

The large, deep penetrating ulcer shown in figure 16, situated on the lesser curvature just proximal to the pylorus, proved to be benign, despite its large size.

Dr. Furey, I will show you an x-ray picture of another ulcer. Can you tell me whether it is benign or malignant?

DR. FUREY: I think it is malignant.

FIGURE 15. Same case as figure 14. X-ray taken 10 weeks later shows no evidence of ulcer. However, at operation two weeks later the ulcer was present and microscopic examination revealed it was malignant. The crater had filled in, giving the appearance roentgenologically of healing.

DR. COLE: Very good! Tell us how you decided that.

DR. FUREY: I saw one quite like it. It is remote from the lesser curvature, to start with, irregular in outline, and there is distinct mucosal pattern change—which to me is characteristic of malignancy. And if you tell me it is benign I will not disagree with you.

DR. COLE: The ulcer crater had the appearance of a benign lesion except for a papillomatous growth in one quadrant which proved to be malignant.

We are now ready for some questions. Dr. Rudolf J. Noer of Louisville, Kentucky, is here, and I would like him to join us.

Questions and Answers

DR. COLE: One of the first questions we ought to ask the entire panel is this: Does a gastric ulcer ever turn into cancer? Dr. Noer, what do you think? How often does a gastric ulcer turn into a malignant ulcer?

DR. RUDOLF J. NOER: I don't think anybody knows. It is a rather academic question, after all. One sometimes sees an ulcer which in every way appears benign until the microscopist says it is malignant. Whether this started as a benign ulcer or, as some believe, as a malignant ulcer is still a moot question. I personally believe that some ulcers do become

malignant after having been benign in the beginning.

DR. COLE: How about you, Dr. Palmer? What is your thinking?

DR. PALMER: I do not think there is proof that any gastric ulcer becomes malignant. On the other hand, I must admit the problem is a difficult one. There are a few instances when at operation or at autopsy one finds benign ulcer and in one edge—and one edge only—there is malignancy. One cannot deny the possibility that this is malignancy developing in the ulcer. The same situation applies to certain scars of gastric ulcer. I think what usually happens in the latter case is that carcinoma develops in the mucosa adjacent to an ulcer, purely coincidentally, and then in time progresses into the ulcer. As Dr. Noer said, the question is really an academic one. The real problem concerns the nature of the lesion at the time you are dealing with the patient.

DR. COLE: Dr. Furey, what do you think?

DR. FUREY: I feel there is only one way to tell, and that is to take out the ulcer and look at it. If you take it out, how can you tell what develops in it later? Subsequent malignancy may develop, possibly around the edges, or a malignancy may be remote from the original ulcer and may extend upward to it. Certainly that would not constitute malignancy developing in an ulcer. My feeling is that I have never seen one.

DR. COLE: Those two panel members were very careful not to make a definite statement. I will try to be more specific. I will admit that less than 5 per cent of gastric ulcers become malignant; maybe it is 1 per cent or 1.5, but I would guess that it occurs now and then.

Let us consider another important point. What percentage of gastric ulcers are malignant? I said I thought it was somewhere between 10 and 24 per cent, and I think I have the statistical data to indicate that. Yet, I know statistics often are misleading. My figure is 15 per cent. Dr. Noer, what is yours?

DR. NOER: I would guess that is about right.

DR. PALMER: I cannot make a guess at that. An ulcerating carcinoma ordinarily looks like an ulcerating carcinoma, as Dr. Furey pointed out, and the diagnostic error is very low because the radiologist calls it malignant and the clinician calls it malignant. Are you including that group?

DR. COLE: I am including all the lesions which have a crater, not the polypoid lesions.

DR. PALMER: I am willing to guess that 25 per cent of those are malignant, which is not to say we do not recognize them as malignant.

DR. COLE: Dr. Furey?

DR. FUREY: I concur in that; I pointed out originally that upward of 5 per cent of so-called benign ulcers—those we recognize and think are benign after exhausting every possible means of examination including gastroscopy and even surgical exploration—would be a fair figure. When you include the group that Dr. Palmer included—that is, the ulcerating malignancies which look like ulcers but actually are ulcerations within a malignancy—certainly 25 per cent is probably conservative.

DR. COLE: He is true to his specialty, is he not? He says they make only 5 per cent error.

DR. FUREY: I did not limit it to my specialty; I included surgical exploration.

DR. COLE: I think all of you have seen articles quoting the roentgenologic diagnostic error at 10 per cent or more.

DR. FUREY: Are you referring to the earlier question about errors in diagnosis?

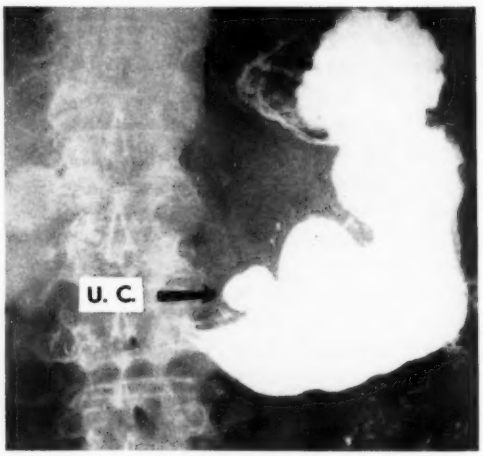


FIGURE 16. Large, deep penetrating ulcer (marked "u.c.") on the lesser curvature just proximal to the pylorus. Despite its large size, it was benign.

DR. COLE: Yes.

DR. FUREY: I will agree with you a hundred per cent on that; I think this is entirely independent.

DR. COLE: How many ulcers diagnosed as benign by the radiologist turn out to be malignant?

DR. FUREY: That is another question.

DR. COLE: I think we have discussed that adequately. We all admit that there is a significant error, yet we cannot arrive at a positive figure.

DR. PALMER: I do not think it is fair to put all the responsibility for diagnosis on the radiologist. There are phases to the analysis other than roentgenologic.

DR. COLE: Yes, but when you start going into the acidity, size, question of hemorrhage, there is not much difference between the two groups.

DR. PALMER: I do not agree with that at all.

DR. COLE: I quoted two or three authorities who made a study of it.

DR. PALMER: I know, but you either misquoted or you misinterpreted them or the authorities were wrong.

DR. COLE: Well, all I could do was give the figures which I found.

DR. PALMER: I would like to back up a bit and make some comments later. There are certain conditions under which it is wrong to make even a tentative diagnosis of benign ulcer, even though the lesion looks benign to the radiologist. One such condition has to do with gastric acidity. If the presence of acid in the stomach is not demonstrable, one has no right to diagnose a benign ulcer. There are no benign ulcers with persistent achlorhydria. There are, to be sure, large numbers of carcinomas with high acid values. Persistent anacidity is incompatible with a diagnosis of benign ulcer. That is just one telltale point, but the combination of complete anacidity and an ulcerating lesion spells malignancy.

DR. COLE: We have many questions to be answered, so let us start with you, Dr. Furey. You answer one and we will proceed that way through the panel.

DR. FUREY: "Is injection of air into the stomach after contrast media practical?" There have been any number of attempts to do that, and it has been practical in many ways. Those of you who practiced medicine years ago remember the seidlitz powders. Recently there has been some attempt to revive their use after giving contrast media, and it has produced some effects which have been revealing in certain instances of gastric pathology. I am not putting in a plug here for a particular soda pop, but 7-Up has been used rather extensively and has served as a double contrast medium in visualizing gastric lesions. Such an exhibit was made at the American Roentgen Ray Society meeting in Chicago in September 1955. It is practical, but not ordinarily considered very necessary, and for that reason I do not believe it will ever be done very extensively.

DR. PALMER: "Can an ulcer patient drink decaffeinated or Sanka coffee?" Yes.

DR. NOER: "Please discuss the statement that the longer the duration of symptoms in cancer of the stomach prior to surgery, the better the prognosis." By and large, this concerns whether a given carcinoma is a slow-growing, slow-developing—in other words, a more mature—cancer in contrast to the embryonal type of rapidly developing, very malignant tumor. That, of course, is related to the statements made earlier on Broders' index. I suppose that, with many reservations, one might say that the longer the duration of symptoms in cancer of the stomach prior to surgery, the better the prognosis. There would be many exceptions to this rule.

DR. COLE: "What is the present status of gastroscopy in distinguishing between benign and malignant crater ulcers?" I am not sure the gastroscopist can be very accurate, because, frankly, I cannot tell when I have the lesion in my hand, unless it has a little hyperplastic area in the crater. We often employ gastroscopic examination, but I know it carries a high incidence of error.

DR. FUREY: Dr. Cole, before the next question, which has to do with gastroscopy, I want to thank you for defending my position. You make the point that you cannot tell in some of these cases whether or not they are malignant even when you have the lesion in your

hand. How, then, can I tell by looking at a mere shadow of such a lesion?

DR. COLE: Of course, you cannot tell; I think you do very well.

DR. FUREY: This question has two parts. (1) "Do you advise routine gastroscopy of ulcer craters on the lesser curvature?" Personally, we do not. Whenever we have any reason, however, to suspect something other than benignancy, we certainly do. I saw a patient just today whose ulcer crater had disappeared entirely but who has been running persistent blood. An x-ray examination six months ago was absolutely negative. The ulcer cleared in two weeks on medical management, but because of the persistence of bleeding and because the man is 74 years of age, we certainly advise gastroscopy in his case.

(2) "What is your opinion of biopsy?" I think I made that perfectly clear. When there is any question of distinguishing between benignancy and malignancy—whether it be the radiologist, the internist, the surgeon or anyone else—exploratory laparotomy is absolutely indicated, and we should not limit it to biopsy. I think surgery should be done even if it is a benign lesion at that time, because there is only one way to tell, and that is to examine it microscopically.

DR. PALMER: I believe the gastroscopist can tell more than you give him credit for. The fact that frequently you cannot differentiate a benign ulcer from a malignant ulcer when you feel it from outside the stomach or when you take it out and hold it in your hand and look at it does not mean that the gastroscopist may not have some advantage over even those types of visualization. I am convinced that when a gastroscopist is able to see an ulcer he very frequently can detect things about it that are significant in determining whether it is benign or malignant. I do agree with Dr. Cole that there is a diagnostic error in gastroscopy. There is a diagnostic error in roentgenology, in clinical appraisal, in the surgeon's appraisal when he feels the stomach; there is a diagnostic error when the stomach is opened and examined in the laboratory. The question is, How far is one going to go in a given instance?

I have a question or two having to do with this. First, "What is the place of the gastroscopic biopsy in gastric ulcer?" The question pertains to biopsy through or with the so-called operating gastroscope. In the hands of Dr. Benedict in Boston it has been quite successful. We have not used it. Other workers have been somewhat hesitant or reluctant to introduce it for various reasons, one of which is the difficulty in getting the jaws of this operating gastroscope to the site of the lesion.

"Is the length of time for medical management three weeks or six weeks?" I would be heretic enough to say, give your patients six weeks before consigning them to the surgeon. I know that sounds bad to my surgical colleagues, but if the lesion is a rapidly metastasizing carcinoma you cannot do anything anyway. If the lesion is a slow-growing carcinoma, one has time.

One more thing about the question of age. Benign ulcers are very common in the older age groups, as are malignancies.

DR. COLE: Dr. Noer, that gastroscopic question seems to have broad interest. Do you want to comment on it?

DR. NOER: My experience with gastroscopy has been probably one of the most disappointing of all the experiences I have had with diagnostic procedures. I have always felt that it ought to be very helpful, but my personal experience with even supposedly expert gastroscopists has been most disappointing.

Further, I would like to say something else about gastroscopic biopsy. I would have the same lack of faith in the effectiveness of gastroscopic biopsy that I have in biopsy taken in the operating room. In a situation where there is a large ulcer on one side and a very small new growth on the other side, it would be very easy to get a biopsy specimen from a place far away from a carcinoma which was present and growing.

DR. COLE: Dr. Noer, you intimated that the section from the operating table under frozen section is unreliable. Yet if you found a lesion up near the cardia, you would take it out for pathologic examination before doing a total gastrectomy, would you not?

DR. NOER: Yes, I would.

DR. COLE: Accordingly, then, if the pathologist said he could not see any evidence of cancer, you obviously would not do total gastrectomy. After the ulcer was excised and diagnosed microscopically as benign, and the opening closed, what then would you do surgically? Would you do a gastrectomy? Would you do a gastroenterostomy after having excised the ulcer, which supposedly is benign and is high up in the cardia?

DR. NOER: What you are saying, first of all (and I agree), is that I would not like to do a total gastrectomy unless the indication were very real. The way you gave the question, one would not want to do a total gastrectomy. In the case you describe I probably would do a high subtotal gastrectomy, recognizing that I might decide to go back if, within a day or two, the pathologist found some carcinoma. I might go back and do a total gastrectomy.

DR. COLE: Suppose you know it is benign (and here is where the surgeons disagree), benign and high up, which operation would you prefer if you were the patient? Would you prefer local excision and gastroenterostomy, local excision and subtotal gastrectomy, or any other?

DR. NOER: I would prefer, I think, a subtotal gastrectomy. You have already done the local operation, and excised the ulcer.

DR. COLE: What would you want done, Dr. Palmer?

DR. PALMER: I agree with Dr. Noer—subtotal gastrectomy, removing the lesion.

DR. COLE: The lesion is already out.

DR. FUREY: Not being too well versed in this surgical procedure, I have the feeling that the surgeon should be guided entirely by what he sees at the time and what he himself thinks. I personally feel that if it is warranted that you go in a second time on a patient who has been resected and you change your mind, or if you have had local resection of the ulcer and decide you have to do something—

DR. COLE: Wait, this is an ulcer and we know it is benign.

DR. FUREY: I agree that if you find it is necessary you are going ahead, after having taken it out, so I do not know why you did not do it in the first place.

DR. COLE: Would you do a subtotal?

DR. FUREY: I would do a subtotal if I were surgically inclined.

DR. COLE: I think we are agreed on that. What about leaving the ulcer in?

DR. NOER: No.

DR. FUREY: Don't you agree that if you are going to do a biopsy on such a lesion you might remove the entire lesion and do the biopsy on that?

DR. COLE: That is right.

DR. FUREY: I do not believe in any biopsy other than the total removal of the lesion itself, unless it is one of those extensive situations that I discussed.

DR. COLE: We all agree there is no place for an operation which leaves the gastric ulcer *in situ*.

DR. NOER: "Does vagotomy have any place in the treatment of gastric ulcer?" In my judgment, no.

DR. COLE: We all agree on that.

I have two questions which are almost identical. "Is there any place for less than a radical resection of gastric cancer?" "How extensive a resection of tissues and organs around the stomach do you do when you discover by frozen section or other means that a given ulcer is malignant? Also, how about total gastrectomy as opposed to radical?" I would do the same operation for a malignant crater ulcer as I would do for a polypoid carcinoma, i.e., a high subtotal, keeping far away from the ulcer. If it is up so far that I cannot get 5 cm. or more above it without doing a total, then I would do a total, because I do not think it does any good to take out these malignant ulcers with a half-inch margin. That is just playing with fire. In other words, one must get widely around the lesion, and if this means doing a total, then there is nothing else to do. But remember that it is even more important to get the gastrohepatic omentum with its nodes—that you must do, even with a subtotal gastrectomy. No operation is complete unless you have all the gastrohepatic omentum with all the nodes you can find around the celiac axis, which is where most nodes will be located.

DR. FUREY: I am assuming this next ques-

tion has to do with subtotal gastric resection rather than simple resection. "Dr. Strode of Honolulu and others lean toward the idea of resection in all ulcers." My position certainly is that resection in all ulcers is not indicated. Those patients who have recurrences over too long a period or in whom ulcer persists or there is suspicion of malignancy should have resection, but the mere finding of an ulcer crater is not, in my opinion, an indication for resection.

DR. PALMER: "How accurate do you believe cytologic studies are in early gastric malignancy diagnosis?" We have been surprised at their accuracy in the past two or three years. I would say 80 per cent, perhaps even 90, in sufficiently well-trained and skillful hands. We have seen the cytologist make a diagnosis of carcinoma of the stomach when the radiologist, the gastroscopist and even the surgeon at the operating table had difficulty in finding a lesion; carcinoma was demonstrated by the pathologist.

DR. COLE: Is that with the use of the Papanicolaou, balloon, or what other mechanism?

DR. PALMER: We do not use the balloon; it is a modified Papanicolaou stain, washing of the stomach, sedimentation, staining, and studying the slide for neoplastic cells.

DR. COLE: We all agree that is pretty accurate.

DR. NOER: I was impressed with Dr. Palmer's statement about the patients whom only the cytologist could diagnose as having carcinoma. I wonder whether we are not dwelling excessively on the possibility of preoperative diagnosis of cancer of the stomach. An internist friend of mine told me about three patients he had within a few months of each other who completely changed his viewpoint on treatment of gastric ulcer. All three cases were diagnosed by the internist and by the radiologist as benign. In all, the size of the ulcer decreased on medical therapy, but the lesions failed to disappear within a reasonable length of time and all the patients underwent operation. All three of them were diagnosed as benign ulcers at the operating table by the surgeon. All three were diagnosed as benign by the pathologist in the laboratory. Of course you know what I am leading up to. All three ulcers were malignant when examined histologically. It seems to me that the crux of this whole matter is that if a gastric ulcer does not clear up quickly under a nonoperative regimen we cannot afford to take the responsibility of delaying too long.

DR. PALMER: There are other responsibilities too. I can cite three patients who died this summer from subtotal resection for benign ulcer.

DR. NOER: I would have to agree that that is just as fatal as the cancer.

DR. COLE: Recently I operated on a patient who had had ulcer symptoms for 11 years. Somewhat to our surprise, he had an inoperable carcinoma of the stomach which had invaded so widely I could not touch him; so that is one rebuttal, in a way.

DR. NOER: Don't you think that all of us doing surgery see a number of patients every year who have been temporized with, who turn out to have inoperable cancer? I know I do.

"What percentage of the cortisone-produced ulcers are malignant?" My guess would be that all are benign. They are acute, recent ulcers, I believe.

DR. COLE: "Please discuss differential diagnosis, 60 year old man; melena, four hemorrhages past eight years; never had any pain; x-ray diagnosis, cicatricial deformity of the duodenum." The answer appears obvious. I suppose there is a trap here, but I will say the patient has a duodenal ulcer with hemorrhage, which may or may not clear with proper medical therapy. Even though I may present a rather radical viewpoint on ulcer, I always say that patients with duodenal ulcer should have medical treatment first unless they are perforating or having a severe hemorrhage which is out of control. This appears to be a duodenal ulcer, and therefore the chance of cancer is unlikely.

DR. FUREY: I would like to comment on that. I think there are certain patients who are inclined to have hemorrhage. I have one patient in mind in particular, a physician. He was 20 years old when he had his first hemorrhage, and he is now 57 and has had hemorrhages off and on through all those years.

Last year he had subtotal gastric resection, and his ulcer was one of those benigns that Dr. Palmer said one does not see very often. He did have a gastric ulcer at the time of operation. In spite of the resection, the gastric ulcer has recurred, and on top of that he has had two hemorrhages since then.

Dr. Cole, I have one question I can answer and about which there is no argument. "What happened to the patient who ruptured barium into the peritoneal cavity?" The patient was operated on immediately, and died within 48 hours. Barium in the peritoneal cavity is a poisonous substance, for some reason. Dr. Leo Rigler of the University of Minnesota pointed out some years ago that there was a high percentage of deaths following administration of barium enemas to patients with perforated colonic diverticula, and the only thing they could attribute it to was barium.

DR. PALMER: "What is the physiologic relationship between achlorhydria and carcinoma of the stomach?" No one is in a position to answer that. It is a very intriguing problem. There are those who think there is a definite relationship, but one can demonstrate areas of atrophy histologically in almost all stomachs, certainly in persons over the age of 40 years, so we do not really know what significance this has. That is, we do not know the true relationship of gastric atrophy, atrophic gastritis and carcinoma. Similarly, we do not know the relationship of achlorhydria to carcinoma, except that about 40 per cent of patients with carcinoma do not have free acid in the gastric content. A very significant item is the fact that 60 per cent do, and they may have high free acid values.

"Does radiation therapy for presumed benign gastric ulcer, if leading to anacidity, actually predispose to gastric malignancy?" Nobody knows. We have been employing this therapeutic method since 1937, almost 20 years. We have carefully followed the 1500-odd patients who have received this therapy and have not found any increased incidence thus far of gastric cancer in the group. More time and study, of course, will be required to answer the question.

DR. FUREY: May I make a point on that? One thing that has come up with reference to use of x-ray in therapy and the eventual occurrence of malignancy has been in the instance of thymus gland. I give that only as one example of the things we used to do and which apparently have been followed by some bad results. I think this question is unfair, for one reason. These patients are beyond the stage where x-ray might have much effect on the tissue changes as they go along. These patients are all well beyond maturity; they are in the age group where one does not get the changes that occur in an infant, and for that reason I think the possible incidence of malignancy would be very low.

DR. PALMER: Yes. "Do you use irradiation routinely in the treatment of benign peptic ulcer?" We use it almost routinely in duodenal ulcer. We use it in gastric ulcer only when we are very sure of our diagnosis of benignancy. I might point out that there are no pathognomonic criteria of benignancy; there are pathognomonic criteria of malignancy. This may seem a strange statement, since I have been defending the diagnostician's ability to recognize benignancy when he has the evidence all together and follows the patient for a given period. It is important, however, to point out and recognize that there are no pathognomonic signs of benignancy and there are many pathognomonic signs of malignancy.

"Why is this treatment, namely, radiation therapy, not used more often in the United States?" That is our fault and also the fault of the therapy in the sense that we have not urged its use; it is not good enough and we do not know enough about it. In the great majority of patients treated with radiation therapy, the acid level drops 50 per cent or 80 per cent or 100 per cent for a few weeks and then gradually returns. After six months it is half-way back to normal, perhaps, on an average, and at the end of a year it is likely to be normal, that is, at a hypersecreting level for a patient with duodenal ulcer. There is great variation, some having longer achlorhydric intervals and some shorter. To sum it all up, we have thought that the help obtained from the procedure has been sufficiently worth-

while for us to continue its use, but it is certainly not the final answer to the problem.

"Is there any survey over a long period of years of the therapeutic value derived from x-ray radiation of the stomach in the treatment of gastric and duodenal ulcer?" The paper I referred to earlier, by Kirsner, Levin and myself (published in the J.A.M.A. in December 1954), dealt with a series of 121 patients so treated for gastric ulcer. As I pointed out, there were five errors, and we are in the process of analyzing our results with over 1000 patients with duodenal ulcer.

DR. NOER: "What has been your experience with regard to linitis plastica, resectability and curability?" My experience has been so limited I would hesitate to answer. One case which I did not personally do but which I saw was diagnosed at the operating table and by the pathologist as linitis plastica and was eventually diagnosed histologically as syphilis of the stomach.

DR. COLE: My experience with linitis plastica has been unfavorable. I do not like that lesion. It grows right up into the esophagus, and one has to take out half the esophagus to get it all out.

"Can you comment on the prognosis of leiomyosarcoma of the stomach?" Contrariwise, that is remarkably amenable to treatment, and the five year survivals will be as high as 30 to 40 per cent. I cannot say that from my own experience; I am really quoting what I read in the papers, like Will Rogers. Dr. Noer, is that your experience?

DR. NOER: Yes.

DR. COLE: Any comments from any other panel member?

Gentlemen, I think we have exhausted our audience.

41st Annual

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

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The Management of Angina Pectoris

The importance of patients understanding the cause and mechanisms of their symptoms; where indicated, the induction of hypothyroidism by means of radioactive iodine.

A. CARLTON ERNSTENE, M.D.

Chairman, Division of Medicine, Cleveland Clinic, and Chairman, Section on Internal Medicine, American Medical Association, 1956-7

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ASPIRIN POISONING

THE American people spend a great deal of money on medicines. In 1951 the public spent about three-fourths of a billion dollars on prescriptions and a full billion dollars on packaged medication, of which 135 million dollars went for aspirin and analgesics. This means that practically every household has some type of pill or medicine around. Too frequently adults assume that these drugs are harmless and leave them where young children can easily reach them.

Dr. Katherine Bain of the United States Children's Bureau has recently shown that the death rate of infants under five years of age from the ingestion of a poison is four times higher than the British rate. Death rates in the United States and Great Britain are generally comparable, and such a great difference for one specific rate was carefully analyzed.

Food is no longer a common source of poisoning. In the two years under investigation only eight deaths due to this cause occurred, and these were attributed to such substances as wild berries, toadstools and green pecans. Slightly less than a third of the deaths were due to drugs or medications. A little more than a third were due to general household items such as bleaching agents, furniture polish and moth balls. A quarter were due to petroleum products, principally kerosene. Five per cent of the deaths due to poisoning in the home were unclassifiable because of insufficient data on the death certificates.

Some of the drug poisoning in small children results from overdosing, but a great deal of it is like any other household poisoning—the child simply swallows something he has found. The most common drug offender in this age group is aspirin. The flavoring of aspirin tablets for children has increased the incidence of poisoning to an alarming degree. The flavor is so good that children search every nook and corner for this "candy" aspirin.

In the first 500 cases of poisoning reported from the Chicago Poison Control Center, 17 per cent were due to aspirin ingestion. Of 429 poison cases reported from eight District of Columbia hospitals in 1954, 118 or 27 per cent were due to aspirin. In 20 years the death rate from salicylic compounds has increased from 30 to 130.

A concentrated effort by every physician to educate parents to the dangers of accidents and poisons in and about the home is necessary on the local level. This can be done by pointing out corrective measures while making home calls, by distributing and insisting that mothers read child-safety booklets, and by using a bulletin board in the office to highlight accidents and poisonings that occur in the community each week. Lastly, much can be accomplished by getting the cooperation of the pharmacists in putting a label, such as "Keep out of the hands of children," on all dangerous drugs and agents.

JAY M. ARENA
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HEART DISEASE

THE battle against heart disease today is a race against time. While the fight goes on, men, women and children—especially children—are dying too soon. Everyone knows that heart disease is now our number one killer—truly the captain of the men of death. Every 45 seconds some one of us dies of heart disease. In any year almost 800,000 people die of a cardiovascular disease—at least half of all who die in our country. One-third of these deaths from heart and blood vessel diseases occur in people under 65 years of age. One out of every 15 of us has a disability related to the heart.

The statistics of heart disease are startling but they have not startled us enough. They are figures charged with emotion. They represent pale, weak little children with rheumatic fever, short of breath, with solemn little faces sometimes wrung with anguish, often unable to play or to keep up in school with their brothers and sisters and friends. They represent men and women with the headaches, and fears and tensions of high blood pressure. They signify executives and foremen and statesmen and leaders suddenly stricken with the terror of angina pectoris or the sudden collapse of coronary thrombosis. And they mean fathers and mothers and friends and associates worried and distressed and watching—constantly watching to make sure that the one with heart disease doesn't become exhausted, doesn't overdo, doesn't work too hard, doesn't run or jump or lift or pull or push. The lives of the sick are short and punctuated by innumerable don'ts.

The infectious diseases are being controlled through the progress of medical science, but research is apparently more difficult in conditions affecting the heart and blood vessels. The approach to these conditions is on a far broader front. The history of medicine shows that knowledge of causes and mechanisms leads to specific methods of treatment and cures. We do not know the cause of rheumatic fever nor can we say with certainty how the condition attacks the muscle of the heart. All civilized races and nationalities are apparently susceptible to rheumatic fever and rheumatic heart disease. We have no specific diagnostic test for rheumatic fever as we have tests for typhoid fever, syphilis, pneumonia or diphtheria. For many infections specific causative organisms have been found. To rheumatic fever we relate a *Streptococcus* and infections of the throat. But how does this *Streptococcus* cause rheumatic fever in some people and not in others? Perhaps there is an allergy, perhaps some other causative agent or condition needs to be associated. The answers to the questions of specific causation and specific mechanisms must come from research. When the knowledge is found it will be worth all it can cost.

Recently the American Foundation published two important volumes dealing with a survey of medical research during the half century from 1900 to 1950. Medical leaders participated in charting our progress with a view to forecasting the future. They found that fundamental research oriented toward problems of the rheumatic syndromes may lead to clarification of conditions involving degenerative, inflammatory and death-dealing changes not only of the type of arthritis and rheumatism but also of muscles, bones and lymphatic tissues. The knowledge gained from research on rheumatism may solve myasthenia gravis, muscular dystrophy, multiple sclerosis.

The human body is a great complex of varied tissues closely related in innumerable activities. What we learn about hypertension and hypotension may solve the mechanism of shock, of coronary thrombosis, brain hemorrhage, and serious conditions as yet not fully solved affecting the eyes, the ears and the kidneys, and even the toxemia of pregnancy.

Detailed study of the *Streptococcus* as a factor in rheumatic fever was begun in the Rockefeller Institute in 1919, some 37 years ago. Workers have studied the nutrition, the cellular composition, the various toxins produced by the *Streptococcus*, and the responses of the cells of the body to these organisms. Other students have classified various forms of streptococci. Chemical and biologic studies have been made and all sorts of devices have been used to get at the secrets of this ubiquitous and dangerous organism.

The earliest studies made on the use of ACTH and cortisone showed that these agents could allay the deadly inflammation of the heart that in past years has killed thousands of children almost before medical attention—frequently frustrated and inadequate—could be applied. From the Department of Pediatrics of New York Hospital and Cornell Medical Center, Drs. May G. Wilson and Wan Ngo Lim[1] now report a comparison of 100 patients with rheumatic carditis treated with digitalis and salicylates and other methods usually followed, with 55 patients treated with ACTH and cortisone. In the latter group signs and symptoms of active inflammations of the heart were arrested within 24 to 72 hours. In the majority of the patients enlarged chambers of the heart were reduced to normal. Previously the terrible damage done to the heart in these first few days resulted in irrecoverable damage. Dr. Wilson writes: "There was no overt evidence of residual damage in 84 per cent of the patients who were having their first attack of carditis and who were treated with the hormones."

In her stimulating article Dr. Wilson says: "It would be most gratifying to be able to explain fully these dramatic results but at the present time it is not possible to discuss the mechanism of hormone therapy in active rheumatic carditis. The nature of the chemical reactions involved in the rheumatic process is obscure."

Almost half of the deaths from cardiovaseular disease are due to arteriosclerosis; 30 per cent to arteriosclerosis combined with hypertension. What is this condition? Is hardening of the arteries just a part of the process of growing old? Probably not, because some young people have it. Many old people die without it. Today interest centers on arteriosclerosis of the blood vessels in the heart, the brain and the kidney. This change in the coronary vessels of the heart is the chief cause of death of American men during their period of highest earning capacity. This statement is a fact in a field where many facts are lacking.

Coronary disease is an enemy whose approach cannot be detected and which is known to be lurking ready to strike. We need basic science research into the cause, the mechanisms, the significance of stress and of diets high in fat and of a wide variety of diets under varying conditions. This is long-term research. War can make a whole nation starve for fats but who is going to make America overnight change all its dietary habits for enough years to produce significant physiologic changes in tissues?

Today the word research has become a term with which to charm and work magic. It has been applied to every type of activity from looking up a word in a dictionary to the kind of surveys that are made by advertising agencies in order to find out which television program is drawing the most listeners who stick to the program during the commercial. Similarly in medicine and in biology the word research has come to mean many things to many different people. Some research is carefully planned, organized and co-ordinated; other investigators insist that research cannot be planned but having once begun, the research worker follows an uncharted course. Some claim that the research worker must serve as an individual; others point to the value of teamwork in reaching a conclusion. No doubt some truth is inherent in all of these concepts. Certainly in the magnificent results that have been achieved in the field of infantile paral-

ysis, the National Foundation for Infantile Paralysis has extended its research support to problems that are fundamental to understanding not only the epidemiology and immunology of the viruses of infantile paralysis but also into the nature of viruses generally and into the way in which the virus reaches the cells of the body that it affects; into the chemistry and physics of the changes that go on in the virus and in the cells under numerous circumstances. That experience may encourage other agencies to support basic science research.

MORRIS FISHBEIN

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THE PSYCHIATRY OF GERIATRICS

"Geriatrics" for April 1956 is devoted to a symposium on "Problems of the mind in later life." I do not like the title for I would prefer to say simply "the aged" rather than " in later life." The number of persons in the United States over 65 years of age now approximates 13 million. The number of patients over 65 in mental hospitals has increased 10 times since 1900. Dr. Karl Bowman[1] points out that the gradual diminution of sight and hearing in the aged causes many to withdraw from life somewhat depressed and embittered. The loss of teeth interferes with the eating of proper food. Many old people refuse to wear proper spectacles or hearing aids and, for a number of reasons, many cannot acquire proper dentures. These situations give rise often to emotional reactions. Modern cosmetics are an aid to improved appearance but dyeing of hair and rouging of wrinkles fool few observers. The attitudes of associates and friends may lead to emotional conflicts and feelings of inferiority.

According to the Kinsey reports about 50 per cent of men at age 65 are relatively or completely impotent; women begin to lose interest and have what Bowman calls "a noticeable drop in sex capacity." These conditions lead definitely to mental depression. Indeed, feelings of inadequacy probably explain and underlie the attacks made by elderly men on little girls. Certainly not all old people react in the same way and many find in advanced years a serenity and freedom from disturbing urges which are welcome.

In his consideration of the mental processes associated with aging, Bowman recognizes the wide variation that prevails in loss of mental faculties. Many people aged 60 to 80 are still actually faster in their mental processes than the average.

Oxygen consumption decreases as we grow older and throughout life the rate is higher in men than in women. This, Bowman believes, may explain why women live longer than men. Observation establishes that exercise aids maintenance of good physical condition; similarly mental activities which are carried out regularly and habitually tend to be preserved and to decline more slowly. Memory shows a progressive loss from about 30 years of age onward; learning ability decreases with advancing years; reasoning ability and perception of spatial relations deteriorate with age. Verbal ability decreases less with age than do most other abilities. Finally, imagination, judgment and wisdom are variables; some old people display great wisdom and profound judgment; others seem to both think and act foolishly.

Dr. Bowman emphasizes that society spends largely for rehabilitation of the handicapped but does little to utilize the services of those slightly handicapped by age. He estimates that premature retirement causes an annual loss of output in industry of over five billion dollars. Moreover, forced retirement of persons of superior capacities leads to forced deterioration and emotional disturbances that are costly to the family and society. The psychiatry of geriatrics is in its infancy.

MORRIS FISHBEIN

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